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DECREASED DEXTROSE TOLERANCE IN ACUTE INFECTIOUS DISEASES

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Transient glycosuria has been noted in various infectious diseases. Hibbard and Morrissey [1] found it in diphtheria. Cammidge [2] stated that it occurs in diphtheria, scarlet fever, typhoid fever, influenza, appendicitis, measles and infections with suppuration. Buhl [3] described its occurrence in Asiatic cholera. Castellani and Willemore [4] and Harrison [5] have found that it may be present in malaria. Cammidge [6] and Higginson [7] have designated as "sapraemic glycosuria" that accompanying carbuncle or gangrene. This glycosuria is accompanied by a hyperglycemia according to Hollinger.[8]

A lowered dextrose tolerance was demonstrated by Hamman and Hirschman [9] in lobar pneumonia and acute tonsillitis. Olmsted and Gay [10] found abnormal blood sugar curves in many conditions including those resulting from acute infectious toxins. Tisdall, Drake and

From the John McCormick Institute for Infectious Diseases.

1. Hibbard, C. M., and Morrissey, M. J.: Glycosuria in Diphtheria, J. Exper. Med. **4**:137, 1899.

2. Cammidge, P. J.: Glycosuria and Allied Conditions, London, E. Arnold, 1913.

3. Buhl: Mitteilungen aus der Pfeuferschen Klinik; Epidemische Cholera, Ztschr. f. rationelle Med. **6**:1, 1855.

4. Castellani, A., and Willemore, J.: Glycosuria of Malarial Origin, Brit. M. J. **2**:286, 1921.

5. Harrison, G.: Glycosuria of Malarial Origin, Brit. M. J. **2**:630, 1921.

6. Cammidge, P. J.: Sapraemic Glycosuria, Brit. M. J. **1**:511, 1921.

7. Higginson, C. G.: Sapraemic Glycosuria, Brit. M. J. **1**:296, 1921.

8. Hollinger, A.: Ueber Hyperglycemie bei Fieber, Deutsches Arch. f. klin. Med. **92**:217, 1907-1908.

9. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar: I. Alimentary Hyperglycemia and Glycosuria as a Test of Sugar Tolerance, Arch. Int. Med. **20**:761 (Nov.) 1917.

10. Olmsted, W. H., and Gay, L. P.: Study of Blood Sugar Curves Following a Standardized Glucose Meal, Arch. Int. Med. **29**:384 (March) 1922.

Brown [11] noted a derangement of the carbohydrate metabolism in infants with acute infectious diarrhea. In the study of various infectious diseases Labbé and Boulin [12] found an increase in the height of the fasting blood sugar as well as in the height and duration of the curve after the administration of dextrose. Hector [13] was able to demonstrate considerable disturbance in the carbohydrate metabolism with lowering of the fasting blood sugar during the toxic stage of severe diphtheria. The studies of Andresen and Schmidt [14] revealed an increased blood sugar content in various infectious diseases excepting measles, and generally there were higher values during the febrile or toxic stages, but diphtheria was not studied. From the study of patients with malignant diphtheria, Lereboullet and Pierrot [15] found a hypoglycemia in a high percentage during the period of intense intoxication. Evans, Riding and Glynn,[16] in a study of oral sepsis, presented evidence of a slight but definite lowering of carbohydrate tolerance, which was less in the patients with acute alveolar abscess and was improved by treatment. Likewise, in general sepsis Thomson [17] found a temporarily defective carbohydrate metabolism. In arthritis also a deficient metabolism of carbohydrate has been emphasized by Pemberton and Foster.[18]

These clinical studies have been supplemented and to some extent confirmed by animal experimentation. Rosenthal [19] found in experimental diphtheria intoxication in rabbits a severe disturbance of carbohydrate metabolism which ended finally in a rapid fall of blood sugar. Tisdall, Drake and Brown [20] demonstrated the production of a lowered carbohydrate tolerance in puppies by the subcutaneous injection of large

11. Tisdall, F. F.; Drake, T. G. H., and Brown, A.: The Carbohydrate Metabolism of Infants with Diarrhea, Infections and Acute Intestinal Intoxication, Am. J. Dis. Child. **30**:837 (Dec.) 1925.

12. Labbé, M., and Boulin, R.: Disorders of Dextrose Regulation During the Course of Infections, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:135 (Oct. 30) 1925.

13. Hector, Francis J.: Carbohydrate Metabolism in Diphtheria, Lancet **2**: 642, 1926.

14. Andresen, J., and Schmidt, S.: The Blood Sugar Content in Infectious Diseases, Klin. Wchnschr. **6**:213, 1927.

15. Lereboullet, P., and Pierrot, R.: Glycemia in Diphtheria, Arch. de méd. d. enf. **31**:148, 1928.

16. Evans, W. H.; Riding, H., and Glynn, E. E.: The Influence of Oral Sepsis upon Carbohydrate Tolerance in Non-Diabetics, Lancet **2**:592, 1927.

17. Thomson, D. B.: Influence of Sepsis and Endocrine Disturbances on Carbohydrate Metabolism, Glasgow M. J. **112**:25, 1929.

18. Pemberton, R., and Foster, G. L., quoted by Olmsted and Gay.[10]

19. Rosenthal, F.: Disturbance of Carbohydrate Metabolism in Experimental Diphtheria Intoxication, Arch. f. exper. Path. u. Pharmakol. **75**:99, 1914.

20. Tisdall, F. F.; Drake, T. G. H., and Brown, A.: The Production of a Lowered Carbohydrate Tolerance in Dogs, Am. J. Dis. Child. **32**:854 (Dec.) 1926.

doses of diphtheria toxin. Sweeney and Lackey [21] confirmed these observations on rabbits.

By studying the pathologic changes in the organs of rabbits dying from an enteritidis—paratyphoid B infection, Menten and Manning [22] were able to demonstrate degenerative changes in the islets of Langerhans of the pancreas. Later, by the injection of these same organisms into rabbits, these authors [23] found a marked increase in the concentration of the blood sugar. Similar lesions were found by Thomas [24] in the pancreas of guinea-pigs dying of the same infection. Zeckwer and Goodell [25] observed a rapid rise in the blood sugar level of rabbits following the intravenous injection of certain killed bacteria and with but little change in the blood sugar with other organisms. Charrin and Carnot [26] produced glycosuria in three of twelve dogs by injecting bacteria into the pancreatic duct. Barber [27] observed a hyperglycemia in experimental cholecystitis in dogs.

DIABETES FOLLOWING ACUTE INFECTIONS

It is now generally recognized that there is a marked lessening of dextrose tolerance with infection in diabetes mellitus, and enormous doses of insulin are required to control an acidosis in a diabetic person whose usual endogenous supply would be sufficient under ordinary conditions. Graham [28] has emphasized the frequency with which bacterial infection is the cause of the onset of coma in diabetes mellitus. Most authors give infection a small place as a factor in the etiology of diabetes. Joslin [29] could find a history of an antecedent infection in about 15 per cent of his cases. Peters [30] has reported some cases in

21. Sweeney, J. S., and Lackey, R. W.: The Effect of Toxemia on Tolerance for Dextrose, Arch. Int. Med. **41**:257 (Feb.) 1928.

22. Menten, M. L., and Manning, H. M.: Pathological Changes in Organs of Rabbits Dying Spontaneously from Enteritidis-Paratyphoid B Infections, J. M. Research **44**:674, 1923-1924.

23. Menten, M. L., and Manning, H. M.: Blood Sugar Studies on Rabbits Infected with Organisms of the Enteritidis-Paratyphoid B Group, J. M. Research **44**:675, 1923-1924.

24. Thomas, B. G. H.: Occurrence of Organisms of the Enteritidis Paratyphoid B Group in Guinea-Pigs, J. Infect. Dis. **35**:407 (Nov.) 1924.

25. Zeckwer, I. T., and Goodell, H.: Blood Sugar Studies: I. Rapid Alterations in the Blood Sugar Level of Rabbits as Result of Intravenous Injections of Killed Bacteria of Various Types, J. Exper. Med. **42**:43, 1925.

26. Charrin and Carnot: Diabetes and Microbes, M. Week **2**:259 and 532, 1894.

27. Barber, W. H.: Hyperglycemia Following Experimental Cholecystitis, Proc. Soc. Exper. Biol. & Med. **23**:101, 1925.

28. Graham, G.: The Relation of Infection to Diabetic Coma, Quart. J. Med. **18**:294, 1925.

29. Joslin, E. P.: Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928.

30. Peters, J. P.: The Effect of Infection on Diabetes and Glycosuria, Proc. Connecticut M. Soc., 1923, p. 190.

which the diabetes was preceded by an acute infection. Geyelin [31] stated that he had seen eight cases in which the diabetes arose within five weeks after an acute infection. White [32] in the study of one hundred diabetic children found that only 2 per cent did not have a history of acute infections preceding the onset of the diabetes. It seems to be well accepted that diabetes, even in a fulminating form, can follow acute infectious diseases such as typhoid fever, scarlet fever, cholera, influenza, diphtheria, enteric fever, tonsillitis, malaria, syphilis and rheumatic fever. Patrick [33] reported a case of acute diabetes which followed an attack of mumps, and Gunderson [34] believes that epidemics of mumps are followed by a rise in the death rate from grave diabetes in the young within the three or four years following each successive epidemic. Holcomb [35] reported two cases of diabetes in which the onset was accompanied or preceded by focal infection. Beck and Pollock [36] have observed that pathologic conditions of the ear, nose and throat are not infrequently found in diabetes. In a statistical study of diabetes as compared with other general diseases, Barach [37] found that diabetes was more commonly preceded by chronic tonsillitis, typhoid fever and pneumonia than were other chronic diseases.

It is well known that diabetes mellitus may follow closely or accompany acute pancreatitis. Recently such cases have been reported by Dunn, Vatcher and Woodwark,[38] by Foord and Bowen [39] and by Warfield.[40] Adams [41] thinks that disease of the gallbladder is a doubtful factor in the etiology of diabetes mellitus, but Lichty and Woods [42] expressed the opinion that diseases of the gallbladder and bile ducts

31. Geyelin, H. R., in Cecil, R. L.: Text Book of Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1930.

32. White, P.: The Potential Diabetic Child, J. A. M. A. **88**:170 (Jan. 15) 1927.

33. Patrick, A.: Acute Diabetes Following Mumps, Brit. M. J. **2**:802, 1924.

34. Gunderson, E.: Is Diabetes of Infectious Origin? J. Infect. Dis. **41**:197 (Sept.) 1927.

35. Holcomb, B.: The Influence of Focal Infections in Diabetes as Shown by Alterations of the Blood Sugar Curve, J. Lab. & Clin. Med. **11**:874, 1926.

36. Beck, J. C., and Pollock, H. L.: Pathologic Conditions of the Ear, Nose and Throat in Diabetes, Arch. Otolaryng. **5**:400 (May) 1927.

37. Barach, J. H.: Etiologic Factors in Diabetes, Arch. Int. Med. **39**:636 (May) 1927.

38. Dunn, J. P. S.; Vatcher, S., and Woodwark, A. S.: Diabetes as Sequela to Acute Pancreatitis, Lancet **1**:595, 1926.

39. Foord, Alvin G., and Bowen, Byron D.: Acute Interstitial Pancreatitis in Two Cases of Diabetic Coma, Am. J. M. Sc. **180**:676, 1930.

40. Warfield, L. M.: Acute Pancreatitis Followed by Diabetes, J. A. M. A. **89**:654 (Aug. 27) 1927.

41. Adams, S. F.: Is Disease of the Gall Bladder a Cause of Diabetes Mellitus? Surg., Gynec. & Obst. **41**:75, 1925.

42. Lichty, J. A., and Woods, J. O.: The Significance of Glycosuria in Gall Bladder and Duct Diseases, Am. J. M. Sc. **167**:1, 1924.

may be later complicated by diabetes. They cited three patients who recovered from diabetes mellitus and disease of the gallbladder after operation. Rabinowitch [43] in a statistical study found "nine times as many patients with gall bladder disease had diabetes as had the patients in general." Stansfield and Warren [44] have reported two autopsies on diabetic children in which there was lymphocytic infiltration of the islets of Langerhans. Such changes together with the history suggested that the diabetes was of infectious origin.

An explanation for the loss of tolerance in acute infections may be found in the effect of toxemias on the action of insulin. Lawrence and Buckley [45] noted an inhibition of insulin action by diphtheria toxin in rabbits, and sought an explanation in the overactivity of the thyroid-adrenal apparatus. Sweeney [46] observed that injected insulin produced essentially the same effect on the blood sugar of rabbits in the presence of a gradually rising toxemia from diphtheria toxin, and hence concluded that the "effect of toxemia is that of a suppression of endogenous production of insulin." Schwentker and Noel [47] studied the carbohydrate metabolism in children with diphtheria and in rabbits with diphtheria intoxication, and concluded that there is primarily an increased glycogenolysis followed by a decreased glycogenesis, which they ascribed to a suppression of the endogenous production of insulin. They also found that the administration of insulin caused an assimilation of dextrose in such cases.

THE SCOPE OF THE PRESENT WORK

The present work includes: 1. The study of acute infectious diseases in patients by means of dextrose tolerance tests in which 100 Gm. of dextrose in lemonade was given to adults and approximately 1 Gm. per pound to children. The dextrose was given before breakfast or after fasting, and all these patients were given the usual hospital diet for such diseases. The urine was saved in six hour specimens for twenty-four hours, and the amount of sugar was determined quantitatively by the Folin-

43. Rabinowitch, I. M.: The Incidence of Diabetes Mellitus in Diseases of the Gall Bladder and Its Passages, Canad. M. A. J. **14**:296, 1924.

44. Stansfield, O. H., and Warren, S.: Inflammation Involving the Islands of Langerhans in Diabetes, New England J. Med. **198**:686, 1928.

45. Lawrence, R. D., and Buckley, M. B.: The Inhibition of Insulin Action by Toxemias and Its Explanation: I. The Effect of Diphtheria Toxin on Blood Sugar and Insulin Action in Rabbits, Brit. J. Exper. Path. **8**:58, 1927.

46. Sweeney, J. S.: Effect of Toxemia on Tolerance for Dextrose and on the Action of Insulin, Arch. Int. Med. **41**:420 (March) 1928.

47. Schwentker, F. F., and Noel, W. W.: The Circulatory Failure of Diphtheria: II. The Carbohydrate Metabolism in Diphtheria Intoxication, Bull. Johns Hopkins Hosp. **46**:259, 1930.

Berglund [48] method. 2. The determination of the blood sugar of such patients during fasting by the Folin-Wu method. 3. The effect of the administration of dextrose and insulin on acute infections. 4. The production of experimental acute infections in animals and a study of the dextrose tolerance by means of quantitative dextrose determinations on the daily twenty-four hour specimens of urine and by repeated blood sugar curves.

ACUTE INFECTIOUS DISEASES

In table 1 are summarized the results of the study of one hundred and eight patients, including sixty-seven patients with scarlet fever, seventeen with diphtheria, eight with pneumonia, five with influenza, three with acute tonsillitis, three with measles and one each with erysipelas, encephalitis, mumps, epidemic meningitis and poliomyelitis. Ten normal subjects are also included.

TABLE 1.—*Dextrose Tolerance Test in Acute Infectious Diseases, Febrile Stage*

Disease	Number of Patients	Dextrose, Gm. Excreted in 6 Hour Specimen			Dextrose, Gm. Excreted in 24 Hour Specimen		
		Maximum	Minimum	Average	Maximum	Minimum	Average
Scarlet fever	67	4.41	0.10	0.75	5.51	0.23	1.05
Diphtheria	17	3.08	0.19	0.82	4.46	0.42	1.21
Pneumonia	8	2.30	0.15	0.87	3.50	0.24	1.66
Influenza	5	5.01	0.21	1.26	5.70	0.51	1.71
Miscellaneous*	11	6.94	0.14	1.28	7.31	0.23	1.61
Normal	10	0.18	0.04	0.11	0.42	0.13	0.31

* Acute tonsillitis, measles, erysipelas, encephalitis, mumps, epidemic meningitis and poliomyelitis.

The patients with scarlet fever ranged from 2 to 33 years of age. The total amount of dextrose excreted in the urine during the six hour period immediately following the ingestion of dextrose varied from 0.1 to 4.41 Gm., averaging 0.75 Gm. for each patient. In eleven of these patients the amount exceeded 1 Gm. The total amount of dextrose excreted in the twenty-four hours (including the first six hours) immediately following the tolerance test varied from 0.23 to 5.51 Gm. and averaged 1.05 Gm. In thirteen patients the amount for the twenty-four period exceeded 1 Gm., and in twenty-four the values fell within the limits of the normal group. Twenty-four patients each had a sufficient quantity of dextrose in the urine to give a positive Haines test.

Thirty-nine of the sixty-seven patients with scarlet fever were studied again after an interval of from ten to fourteen days following the initial study. The figures for the six hour period varied from 0.02 to 1.6 Gm., averaging 0.15 Gm., and for the twenty-four hour period they were from 0.09 to 1.76 Gm., averaging 0.32 Gm. The results are seen

48. Folin, O., and Berglund, H.: A Colorimetric Method for the Determination of Sugars in Normal Human Urine, J. Biol. Chem. **51**:209, 1922.

in table 2. This same group was studied again from twenty-one to twenty-eight days after the onset of the disease (table 3); in the six hour period the amount of dextrose excreted ranged from 0.02 to 0.27 Gm., averaging 0.08 Gm., whereas the values for the twenty-four hour period ranged from 0.07 to 0.54 Gm., averaging 0.28 Gm.

There were seventeen patients with diphtheria whose ages varied from 4 to 42 years. The total amount of dextrose excreted in the six hour period varied from 0.19 to 3.08 Gm. and averaged 0.82 Gm.; in the twenty-four hour period these values ranged from 0.42 to 4.46 Gm. and averaged 1.21 Gm. The tolerance tests were repeated shortly after the subsidence of symptoms. For the six hour period the figures varied from 0.06 to 0.13 Gm., averaging 0.11 Gm.; for the twenty-four hour

TABLE 2.—*Dextrose Tolerance Test in Acute Infectious Diseases from Ten to Fourteen Days After Admission*

Disease	Number of Patients	Dextrose, Gm. Excreted in 6 Hour Specimen			Dextrose, Gm. Excreted in 24 Hour Specimen		
		Maximum	Minimum	Average	Maximum	Minimum	Average
Scarlet fever	39	1.60	0.02	0.15	1.76	0.09	0.32
Diphtheria	9	0.13	0.06	0.11	0.53	0.16	0.31
Pneumonia	3	0.92	0.10	0.40	2.00	0.21	0.83

TABLE 3.—*Dextrose Tolerance Test in Acute Infectious Diseases from Twenty-One to Twenty-Eight Days After Admission*

Disease	Number of Patients	Dextrose, Gm. Excreted in 6 Hour Specimen			Dextrose, Gm. Excreted in 24 Hour Specimen		
		Maximum	Minimum	Average	Maximum	Minimum	Average
Scarlet fever	36	0.27	0.02	0.08	0.54	0.07	0.28
Diphtheria	2	0.12	0.06	0.09	0.35	0.15	0.25
Pneumonia	1	....	....	0.28	....	....	0.81

period, from 0.16 to 0.53 Gm., with an average of 0.31 Gm. Of these patients with diphtheria, four had dextrose values in excess of 1 Gm. for the six hour period, and in three the value was more than 2 Gm. In three patients the amount fell within the normal range. The urine of eight patients contained a sufficient quantity of dextrose to give a positive Haines test.

The eight patients with pneumonia varied in age from 3 to 60 years. The amount of dextrose in the urine varied from 0.15 to 2.3 Gm., averaging 0.87 Gm., for the six hour period, and from 0.24 to 3.50 Gm., averaging 1.66 Gm., for the twenty-four hour period. Three of these patients were again tested after the crisis. The amount of dextrose in the urine for the six hour period varied from 0.10 to 0.92 Gm., with 0.4 Gm. as the average; for the twenty-four hour period these values were from 0.21 to 2 Gm., averaging 0.83 Gm. In two patients the loss of tolerance persisted long after recovery from the

pneumonia, and it was found necessary to restrict the carbohydrate content of the diet for several weeks. In four cases the amount of dextrose excreted in six hours was in excess of 1 Gm., and in two (both mild cases of bronchopneumonia) the values were normal. Haines' test of the urine was positive in five patients.

Five patients with influenza were studied, and the loss of tolerance in two of these was quite evident. For the six hour period the amount of dextrose excreted ranged from 0.21 to 5.01 Gm., and averaged 1.26 Gm.; the corresponding values for the twenty-four hour period were from 0.51 Gm. to 5.70 Gm., averaging 1.71 Gm. In two of these the quantity of dextrose for the six hour period exceeded 1 Gm., and in two the values were normal. In three patients there was glycosuria.

There were eleven patients in the group classed as "miscellaneous," and the quantitative excretion of dextrose in the six hour specimen varied from 0.14 to 6.94 Gm., averaging 1.28 Gm.; for the twenty-four hour period the figures were from 0.23 to 7.31 Gm., with an average of 1.61 Gm. The patient whose values were the highest had measles shortly after recovery from diphtheria. Another patient with measles excreted 1.01 Gm. of dextrose in six hours and 1.51 Gm. in twenty-four hours. Two patients with acute tonsillitis had dextrose values of 1.62 and 2.73 Gm. for the six hour period and 2.04 and 3.01 Gm., respectively, for the twenty-four hour period. Thus in four of the eleven the amount of dextrose excreted in the six hour period exceeded 1 Gm. Six patients of this group had glycosuria, and in three the values were normal.

Ten subjects without fever and without clinical evidence of an altered carbohydrate metabolism were studied. The values for this group varied from 0.04 to 0.18 Gm. of dextrose averaging 0.11 Gm. in the six hour period; for the twenty-four hour period they ranged from 0.13 to 0.42 Gm., averaging 0.31 Gm. None of these subjects had glycosuria by Haines' test.

In summarizing the study of the patients with acute infections, it can be noted that the most marked decrease in tolerance usually occurred in those who were severely ill or who had one disease followed by complications or sequelae or in those in whom two or more contagious diseases developed in quick succession.

BLOOD SUGAR DURING FASTING

The blood sugar during fasting was estimated in twelve patients with various acute contagious diseases, and the concentration of dextrose varied from 0.097 to 0.145 Gm. per hundred cubic centimeter, averaging 0.115 Gm. The two highest values were obtained in patients with pneumonia.

DEXTROSE TOLERANCE TESTS MADE WITH 0.5 GM. OF DEXTROSE PER POUND OF WEIGHT

These tests were made on eighty-eight patients: fifty-one with scarlet fever, thirty-two with diphtheria, three with measles and two with acute tonsillitis. In this group 50 Gm. of dextrose was given to adults and 0.5 Gm. per pound to children. It was found that the smaller amount of dextrose caused less discomfort in some patients and that the values, although slightly lower, gave a good indication of the patient's tolerance. The six hour period only was used for this group, and the results are summarized in table 4.

The values obtained for patients with scarlet fever were: maximum, 3.85 Gm.; minimum, 0.03 Gm., and average, 0.63 Gm. In nine patients the amount exceeded 1 Gm. and in fourteen the quantity of dextrose was sufficient to give a positive Haines test.

Among the thirty-two patients with diphtheria the maximum amount of dextrose excreted by any one patient in six hours was 4.01 Gm., the

TABLE 4.—*Dextrose Tolerance Test in Acute Infectious Diseases Without Insulin* *

Diseases	Number of Patients	Dextrose, Gm. Excreted in 6 Hour Specimen Without Insulin		
		Maximum	Minimum	Average
Scarlet fever	51	3.85	0.03	0.63
Diphtheria	32	4.01	0.03	0.98
Measles	3	0.99	0.08	0.40
Tonsillitis	2	2.73	0.13	1.43
Normal	4	0.14	0.06	0.10

* 0.5 Gm. of dextrose given per pound.

minimum, 0.03 Gm., and the average, 0.98 Gm. Eleven of these patients had an amount in excess of 1 Gm., fourteen gave a positive Haines test and eight had normal values.

The three patients with measles gave the following results for the six hour period: 0.08, 0.10 and 0.99 Gm. The figures for the two with acute tonsillitis were 0.13 and 2.73 Gm.

Four subjects whose carbohydrate metabolism was thought to be normal were studied, and the values for the dextrose excreted were 0.06, 0.08, 0.14 and 0.11 Gm.

THE EFFECT OF INSULIN

The effect of insulin on the carbohydrate tolerance and also on the course of the diseases, scarlet fever and diphtheria, was studied in twenty-nine patients. The results, both without and with insulin, are summarized in table 5.

Before insulin was given the amount of dextrose excreted in the urine for the six hours after the ingestion of dextrose was: maximum,

6.51 Gm.; minimum, 0.23 Gm., and average, 1.73 Gm. After from 10 to 15 units of insulin was injected, the corresponding values were 3.01, 0.04 and 0.69 Gm. Thus, on the average, more than 1 Gm. of dextrose per patient was utilized on the addition of the insulin. Without insulin, fourteen of the patients had more than 1 Gm. of dextrose in the urine, whereas only six of the same patients excreted more than 1 Gm. of sugar following the injection of insulin. In three patients, however, in whom the course of the disease was fluctuating, the amount with insulin was greater than the amount without it.

An additional group of seventeen patients with diphtheria and scarlet fever was given insulin on the day of admission to the hospital and with the initial dextrose tolerance test. These results are also seen in table 5. The amount in the urine for the six hour period varied from 0.06 to 3.61 Gm., averaging 0.65 Gm., figures practically equivalent to those for the group given insulin with a second dextrose tolerance test.

TABLE 5.—*Dextrose Tolerance Test in Acute Infectious Diseases Without and With Insulin (from Ten to Fifteen Units)* *

Diseases	Number of Patients	Dextrose, Gm. Excreted in 6 Hour Specimen Without Insulin			Dextrose, Gm. Excreted in 6 Hour Specimen With Insulin		
		Maximum	Minimum	Average	Maximum	Minimum	Average
Diphtheria and scarlet fever	29	6.51	0.23	1.73	3.01	0.04	0.69
Diphtheria and scarlet fever	17	....	....	....	3.61	0.06	0.65
Diphtheria and scarlet fever (repeated)	5	6.40	0.37	2.05	1.99	0.10	0.53

* 0.5 Gm. of dextrose given per pound.

Five patients were studied repeatedly by means of the dextrose tolerance test, with and without insulin, and the average amount of dextrose in the urine for six hours was, respectively, 0.53 and 2.05 Gm. By increasing the dose of insulin from 10 to 15 units the average amount of dextrose in the urine was reduced slightly.

Sixteen patients were given from 10 to 35 Gm. of dextrose in addition to the regular diet two or three times daily, and from 5 to 15 units of insulin was injected about twenty minutes preceding the ingestion of dextrose. The clinical course of these patients was followed carefully, and although all these patients made a satisfactory recovery it could not be demonstrated conclusively that their improvement was more rapid than that of similar patients not given additional dextrose and insulin.

EXPERIMENTAL INFECTIONS IN ANIMALS

The tolerance of twenty-nine normal rabbits was ascertained by injecting intravenously at intervals of from three to ten days sufficient 10 per cent solution of dextrose to give a positive Haines test in the

urine. The tolerance was found to vary only slightly in different normal animals and to average 1.0 Gm. per kilogram.

Experimental infections were then produced in twenty-one rabbits by injecting a forty-eight hour broth culture of the organisms into the

TABLE 6.—*Excretion of Dextrose in Experimental Infections in Rabbits and Dogs*

	Broth Culture of Organisms, Cc.	Normal, Gm.	Maximum Dextrose Excreted, Gm.	Minimum Dextrose Excreted, Gm.	Average Dextrose Excreted, Gm.	Animal	Comment
Scarlet fever streptococcus	4- 5	0.030	0.104	0.026	0.059	Rabbit 1	Died after 25 days
Scarlet fever streptococcus	0.5-25	0.036	0.116	0.021	0.060	Rabbit 2	Died after 14 months
Scarlet fever streptococcus	1-55	0.036	0.116	0.011	0.058	Rabbit 3	Died after 13 months
Pneumococcus type I	0.5-35	0.022	0.117	0.023	0.059	Rabbit 4	Died after 6 months
Pneumococcus type I	0.5-40	0.027	0.296	0.027	0.073	Rabbit 5	Died after 5½ months
Typhoid bacillus	0.5-12	0.035	0.126	0.021	0.076	Rabbit 6	Died after 6 months
Typhoid bacillus	1-10	0.040	0.073	0.021	0.044	Rabbit 7	Died after 1 month
Typhoid bacillus	0.5- 5	0.034	0.112	0.015	0.052	Rabbit 14	Died after 5½ months
Erysipelas streptococcus	5-35	0.030	0.160	0.027	0.091	Rabbit 8	Died after 3 months
Erysipelas streptococcus	2-30	0.030	0.096	0.013	0.040	Rabbit 17	Died after 6 months
Influenza bacillus	10-50	0.043	0.091	0.029	0.059	Rabbit 9	Died after 4½ months
Influenza bacillus	1- 6	0,030	0.055	0.035	0.043	Rabbit 15	Died after 3 months
Pneumococcus type III	1-10	0.043	0.169	0.033	0.069	Rabbit 10	Died after 7 weeks
Pneumococcus type III	1-10	0.030	0.125	0.041	0.073	Rabbit 12	Died after 6 weeks
Pneumococcus type III	1- 6.5	0.013	0.076	0.006	0.023	Rabbit 13	Living after 1 year
Scarlet fever anaerobic organisms	0.5-1	0.022	0.044	0.039	0.042	Rabbit 19	Died after 3 weeks
Scarlet fever anaerobic organisms	0.4-2.5	0.026	0.085	0.025	0.050	Rabbit 20	Living after 5 months
Scarlet fever anaerobic organisms	0.2-1.0	0.035	0.062	0.032	0.050	Rabbit 21	Died after 1 month
Scarlet fever anaerobic organisms	0.2-2.5	0.026	0.057	0.017	0.028	Rabbit 24	Living after 4 months
Scarlet fever anaerobic organisms	0.3-1.2	0.023	0.082	0.010	0.040	Rabbit 25	Died after 7 weeks
Paratyphoid B bacillus	0.2-0.6	0.018	0.106	0.034	0.054	Rabbit 26	Died after 1 month
Average		0.030	0.108	0.024	0.054		
Normal values (5 tests)		0.030	0.050	0.010	0.030	29	
Broth injected (5 tests)		0.027	0.053	0.013	0.027	2	
Salt injected (5 tests)		0.030	0.049	0.020	0.030	2	
Typhoid bacillus	0.75	0.007	0.169	0.012	0.077	Dog 2	Died after 17 days
Typhoid bacillus	0.5-7.5	0.060	0.284	0.040	0.158	Dog 3	Living after 9 months

veins of the ear daily in an increasing amount for several days, thence at intervals of two or three days for a few weeks and finally, when a satisfactory dose was established, at weekly intervals for several months. The urine was collected daily and the amount of dextrose

determined quantitatively by means of the Folin-Berglund[48] method, modified by first rendering the urine acid with dilute sulphuric acid. The results of this study can be seen in table 6. The figures recorded are averages for the three days preceding the first injection (normal period) and for two or three days immediately following it.

Scarlet fever streptococci were used in three rabbits, a forty-eight hour broth culture being injected intravenously in amounts varying from 0.5 to 55 cc. In one of these rabbits a subcutaneous abscess was produced by injecting the organisms mixed with sterilized kaolin. A trace of sugar was repeatedly detected by Haines' qualitative test. One rabbit died after twenty-five days, but the other two lived for fourteen and

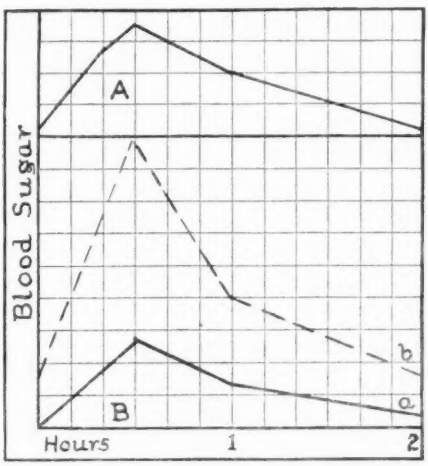

Chart 1.—*A*, blood sugar curve of rabbit 2 on July 25, 1931, one month after an injection of scarlet fever streptococci. Each division on the vertical scale at the left indicates 0.02 per cent. *B*, blood sugar curves of rabbit 3: *a*, curve obtained Dec. 23, 1930, twenty-four hours after an injection of scarlet fever streptococci; *b*, curve obtained on Feb. 23, 1931, twenty-four hours after an injection of scarlet fever streptococci; *c*, curve obtained on July 23, 1931, one month after an injection of scarlet fever streptococci. The divisions on the vertical scale at the left indicate tenths per cent.

thirteen months respectively. The average amount of dextrose excreted was 0.059 Gm. or practically double the average normal value, 0.030 Gm. Repeated dextrose tolerance tests revealed considerable reduction in tolerance. Blood sugar curves are shown for rabbits 2 and 3 (chart 1).

Pneumococcus type I was injected into two rabbits in amounts varying from 0.5 to 40 cc., and sugar appeared in the urine of rabbit 5, the

total amount excreted for one twenty-four hour period being 0.296 Gm. The average amount excreted was 0.066 Gm. daily, or more than twice the normal daily average of 0.024 Gm. Dextrose tolerance tests revealed at times as much as a 50 per cent reduction in tolerance. The blood sugar curve for rabbit 4 is shown. One rabbit lived for six months and the other for five and a half months.

The typhoid bacillus was used for experiments on three rabbits, and amounts of culture varying from 0.5 to 12 cc. were injected. Dextrose

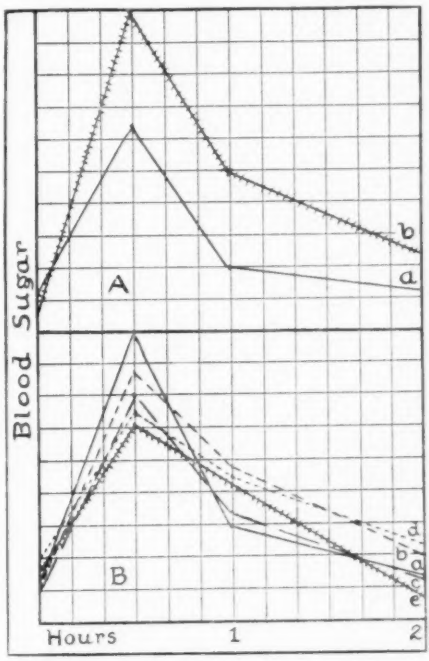

Chart 2.—*A*, blood sugar curves of rabbit 6: *a*, curve obtained four days after infection with typhoid (Jan. 3, 1931); *b*, curve obtained one week after injection of typhoid bacilli (Feb. 16, 1931) when the animal was weak and dying. In this and subsequent charts each division on the vertical scale at the left indicates 0.02 per cent. *B*, blood sugar curves of rabbit 14: *a*, curve obtained before typhoid; *b*, curve obtained two days after the injection of typhoid organisms (April 5, 1931); *c*, curve obtained one week after the injection of typhoid organisms (May 4, 1931); *d*, curve obtained three days after infection with typhoid (May 27, 1931); *e*, curve obtained three weeks after infection (July 13, 1931).

appeared in the urine in quantities sufficient to give a positive Haines test on several occasions with rabbits 6 and 14 and in traces with rabbit 7. Tolerance tests with injected dextrose disclosed a 30 to 50 per cent

reduction in tolerance temporarily. The average daily amount of dextrose excreted in the urine during the forty-eight hours following the experimental infection was 0.064 Gm. Blood sugar curves are exhibited for rabbits 6 and 14 in chart 2.

Two rabbits were given erysipelas streptococcus culture in quantities varying from 2 to 35 cc. A subcutaneous abscess was produced in rabbit 8. A trace of dextrose was detected by the Haines test in the urine of both rabits, and the maximum amount determined quantitatively was 0.160 Gm. in twenty-four hours. The average daily excretion was 0.065 Gm. Rabbit 8 lived for three months and rabbit 17 for six

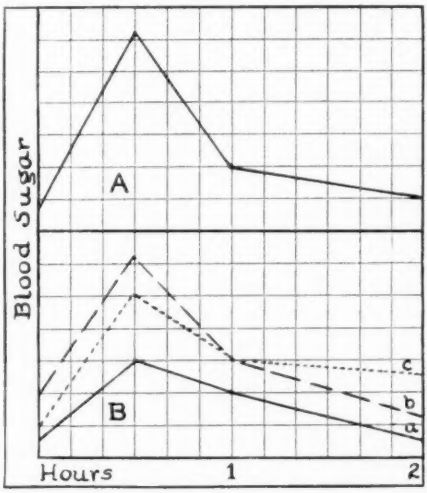

Chart 3.—*A*, blood sugar curve of rabbit 8, thirty-three days after the injection of erysipelas streptococci. *B*, blood sugar curves of rabbit 17: *a*, curve before injection of erysipelas organisms (April 9, 1931); *b*, curve obtained twenty-four hours after the injection of erysipelas streptococci (May 4, 1931).

months. Dextrose tolerance tests revealed about a 25 per cent reduction in tolerance to injected dextrose. Blood sugar curves (chart 3) indicated a slight reduction in tolerance.

Rabbits 9 and 15 were given cultures of influenza bacilli in volumes varying from 1 to 50 cc. An abscess beneath the skin of the back was produced in rabbit 9. Only traces of dextrose were found in the urine, and the average daily excretion was 0.51 Gm. These rabbits lived four and one-half and three months, respectively. Intravenous tolerance tests revealed about a 30 per cent reduction at one time in rabbit 9 but normal values later.

Pneumococcus type III was used with rabbits 10, 12 and 13 in quantities varying from 1 to 10 cc. Dextrose appeared in the urine on one occasion with rabbit 10 and in traces at several times with all three rabbits, and the maximum amount excreted in twenty-four hours by rabbits 10 and 12 was 0.169 and 0.125 Gm., respectively; the average daily excretion of these two rabbits was 0.071 Gm. They lived seven and six weeks. Rabbit 13 was particularly resistant to pneumococci and was less affected than any other of the twenty-one rabbits. The average amount of dextrose excreted per day was only 0.023 Gm. as compared

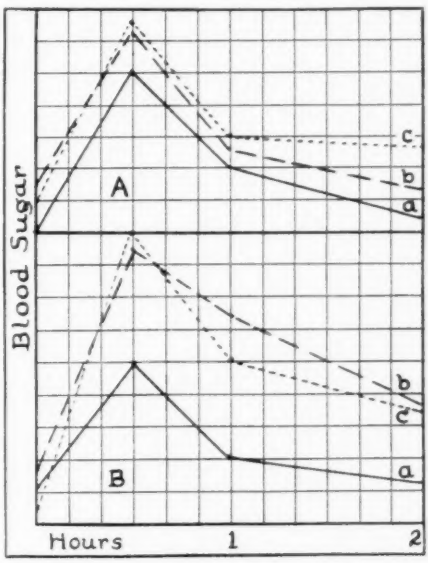

Chart 4.—*A*, blood sugar curves of rabbit 10: *a*, curve obtained before an injection of pneumococci, type III (Jan. 14, 1931); *b*, curve obtained twenty-four hours after an injection of these organisms (Feb. 7, 1931); *c*, curve obtained twenty-four hours after an injection (Feb. 23, 1931). *B*, blood sugar curves of rabbit 13: *a*, curve obtained before an injection of pneumococci, type III (Feb. 3, 1931); *b*, curve obtained twenty-four hours after an injection of pneumococci, type III (April 23, 1931); *c*, curve obtained forty-eight hours after an injection of pneumococci (June 3, 1931).

with the normal 0.013 Gm. The animal is still living after one year. Dextrose tolerance tests indicated slight reduction of tolerance at first, but increased tolerance later. The blood sugar curves for rabbits 10 and 13 are plotted in chart 4.

An anaerobic broth culture was made from the throats of patients with scarlet fever, and quantities of this suspension varying from 0.2 to

2.5 cc. were used to inoculate five rabbits. Three rabbits died after three, four and seven weeks, respectively, and two are living after five and four months. The average amount of dextrose excreted varied from 0.028 to 0.050 Gm., and averaged 0.042 Gm., as contrasted with 0.026 Gm., the average for the normal period. Tests revealed a slight impairment of dextrose tolerance. The blood sugar curves of rabbit 20 are plotted in chart 5.

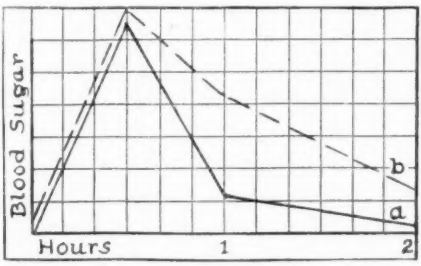

Chart 5.—Blood sugar curves of rabbit 20: *a*, curve obtained before the injection of an anaerobic broth culture from the throats of patients with scarlet fever (Aug. 8, 1931); *b*, curve obtained twenty-four hours after an injection of an anaerobic broth culture (Aug. 27, 1931).

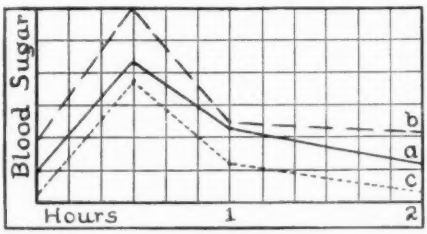

Chart 6.—Blood sugar curves of dog III: *a*, curve obtained before infection with typhoid (April 12, 1931); *b*, curve obtained twenty-four hours after the injection of typhoid organisms (June 17, 1931); *c*, curve obtained five weeks after the injection of typhoid organisms (July 29, 1931).

One rabbit which was given paratyphoid B bacillus lived long enough for study. The average amount of dextrose excreted following the injection of the organisms was 0.054 Gm., and on one day was as high as 0.106 Gm.

Since the typhoid bacillus gave consistently a greater reduction in tolerance than most other organisms, its effect was tried on two dogs for which carbohydrate tolerance was previously determined in the same manner as for rabbits. Dog 2 lived only seventeen days after experiments were begun, and died two days after the first injection, but the

urine contained a trace of sugar on the day following the initial dose. Dog 3 was living nine months after the beginning of the experiment; it was given repeatedly from 0.5 to 7.5 cc. of typhoid organisms, and on many occasions the urine gave a positive test for dextrose. The amount of dextrose excreted varied from 0.40 to 0.384 Gm., averaging 0.138 Gm., for the periods following the injection of the organisms. Dextrose tolerance tests disclosed a moderate reduction in tolerance. The blood sugar curve (chart 6) taken twenty-four hours after the organisms were injected revealed a slight reduction in tolerance, whereas that performed after five weeks indicated a slight increase in tolerance.

Postmortem examination of the animals that died (rabbits and one dog) revealed no gross alteration of the pancreas, but microscopically there was evidence of degeneration in the islets of Langerhans. This observation, however, is somewhat clouded by the presence of postmortem change in some of the animals. That toxic injury to the islet cells can occur in both diabetic and nondiabetic patients has been emphasized by Warren and Root [49] who have described necrosis of the islet cells in pneumonia.

COMMENT

It is obvious from the results of this work that a temporary glycosuria occurs in acute infections and contagious diseases as well as in experimental infections; 41 per cent of the patients with acute infectious diseases had glycosuria when given sufficient dextrose. Likewise, in experimental infections in animals a similar transient glycosuria has been produced. This is accompanied by an increase in the height of the blood sugar concentration during fasting, and by alterations in the blood sugar curves as shown by the dextrose tolerance tests in animals. Thus it is evident that a decreased tolerance for dextrose occurs in acute infections. The decrease in tolerance may last for several weeks or months; six patients—two with pneumonia and four with scarlet fever—required a restriction of carbohydrate in the diet or the administration of insulin to prevent occasional glycosuria. This decreased tolerance can be improved by supplying insulin additional to that produced in the body. This fact is well illustrated in table 5, in which it is recorded that the excretion of dextrose was reduced to about one third of that when no insulin was given. By increasing the amount of insulin and the frequency of its injections the amount of dextrose in the urine was reduced and in all probability the amount of dextrose excreted could have been reduced to normal had the correct amount of insulin been supplied at the proper time. This is evidence that the toxemia of the disease interferes either with the action or the production of insulin or with both of these factors. By supplying exogenous insulin, which

49. Warren, S., and Root, H. F.: Am. J. Path. **1**:415, 1925.

restores the carbohydrate tolerance, it would appear that lack of production is probable. This is supported by the experiments of Sweeney [46] on rabbits given injections of diphtheria toxin and in part by the observations of Schwentker and Noel [47] on both patients and animals.

Histologic study of the pancreas in diabetes mellitus failed to disclose anatomic change in the islets of Langerhans in about 17 per cent of autopsies, according to Warren.[50] That the lack of insulin production may nevertheless occur in such cases is now freely admitted, and also that this lack of function on the part of the islets may occur in toxemias and infectious diseases is well illustrated by the severity of diabetes during infections and its comparative mildness following recovery from the infection. Thus the action of insulin in improving the carbohydrate tolerance in acute infections is analogous to its similar action in diabetes mellitus. In many instances the severity of the disease and the degree of reduction of tolerance could be correlated, and in patients having one contagious disease following another there was marked reduction of tolerance. This suggests a probable important factor in the etiology of diabetes. The recovery of tolerance following injury by infection is explained by immunity to the infecting organism and by regeneration of the islets of Langerhans. The latter fact has been demonstrated to occur in diabetes in which tolerance has been improved.

CONCLUSIONS

1. Glycosuria occurred in 41 per cent of patients with acute infectious diseases. The largest average amount of dextrose was excreted by the patients with influenza and miscellaneous acute infections.

2. This glycosuria is accompanied by a lower carbohydrate tolerance, as shown by dextrose tolerance tests and blood sugar curves both in acute infectious diseases and in experimental infections in animals.

3. Administration of insulin improves the dextrose tolerance in acute infections.

4. This work suggests that in infectious diseases there is often an injury to the islets of Langerhans with a lessened production of insulin.

50. Warren, S.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930, p. 55.

ASTHMA

XVI. TWO HUNDRED AND THIRTEEN "CURED" PATIENTS FOLLOWED UP FOUR YEARS LATER

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In 1928, an analysis of 213 cases in which the patients were relieved of their asthma for more than two years was published in the ARCHIVES.[1] In that article, a clinical classification of the so-called "cured" cases was presented, and a serious attempt was made to define the reason for the "cure." Now, four years later, it is of interest to check up the same 213 cases to see just how permanent the actual "cure" has been and perhaps to throw further light on the mechanism of this "cure." The original article showed the results after two years. Now, an additional four years has been added, and the present article deals with the results six years after the last study and treatment. Very few of the patients have actually been seen or examined at this time, and the following study is based chiefly on letters received from them. If some stress is laid on the incidence of lesions in the nose and throat, it is only because there is reason to believe that such lesions are a handicap in the treatment of asthma.

The gross figures are shown in the accompanying table. It will be convenient to discuss them in accordance with the same clinical classification which was made four years ago.

EXTRINSIC ASTHMA

Pollen Asthma.—Five patients are still free from asthma and hay fever, but at least 4 of the original 13 patients have had relapses, with asthma. All 4 have asthma in the summer, but in 2, within the past year or two, additional attacks have developed after colds in the winter. Three other patients, young men, in recent years, have again suffered from hay fever during the ragweed season. Although they have had no asthma with the hay fever, it is obvious that they are far from "cured." They are listed as having asthma again. All 3 have it in the

1. Rackemann, F. M.: Studies in Asthma: II. An Analysis of Two Hundred and Thirteen Cases in which the Patients Were Relieved for More Than Two Years, Arch. Int. Med. **41**:346 (March) 1928.

summer, but in 2, within the past year or two, additional attacks have developed after colds in the winter.

Lesions in the nose and throat were found originally in only 3 of the 13 cases—infected tonsils in 2 and a cloudy antrum in the third. It is unfortunate that the only patient not heard from is 1 of the 2 with infected tonsils (McG.). The other patient with infected tonsils was not operated on, and she (B.) is 1 of the 2 who now have trouble in the winter. The patient with a cloudy antrum was originally "cured" in some unknown manner; no specific treatment was given, but now he is 1 of those who again have asthma, but only in the summer.

Infected Pollen Asthma.—Only 5 patients in the original large series were "cured," a clear illustration of the obstacle which secondary infec-

Two Hundred and Thirteen "Cured" Cases Followed Again

Classification	Total Cases	"Cured" 1928	Still "Cured"	Asthma Again	Dead	No Answer
Pollen asthma	70	13	5	7	0	1
Infected pollen asthma	39	5	4	1	0	0
Summer asthma (negative tests)	32	10	4	3	0	3
Animal asthma	60	22	19	1	1	1
Infected animal asthma	13	0	0	0	0	0
Mixed extrinsic	121	22	11	7	0	4
Mixed (negative tests)	37	18	10	7	0	1
Special	53	17	11	5	0	1
Total extrinsic	425	107	64	31	1	11
Bacterial asthma	202	25	16	3	3	3
Bacterial asthma (children)	90	34	23	7	0	4
Reflex (not nose and throat)	66	18	9	4	0	5
Reflex (nose and throat only)	10	10	6	3	0	1
Cardiac	56	1	0	0	1	0
Bronchitis and emphysema	45	3	1	0	1	1
Total intrinsic	499	91	55	17	5	14
Unclassified	150	15	12	1	0	2
Total	1,074	213	131	49	6	27

tion puts in the way of successful treatment. Four of the 5 are still well, and the only patient with trouble is Mrs. W., whose badly abscessed teeth were extracted nearly ten years ago. After the extraction, she remained well for eight years, but two years ago, asthma again developed. It is not unlikely that a new focus of infection has developed in the interim. No foci were observed in the other 4 cases.

Summer Asthma with Negative Tests.—Only 7 of the original 10 patients have been heard from, and of these, only 4 are still free from asthma. Of the other 3, R, who is now a college student, was operated on for appendicitis in the summer of 1928 and had a bad attack of asthma during his recovery, but during the four years prior to the operation and the three years since then, he has had no trouble. D., who had trouble every June, has done well for a total of six years, except for an isolated attack in June, 1928, and another attack in the

summer of 1930. In C. asthma has developed at other seasons besides the summer. Unfortunately, the child with the barrel-shaped chest cannot be traced.

Animal Asthma.—This group is an important and fundamental one. Unfortunate as it may seem, there is only 1 patient in the total number of 60 who was formerly sensitive to an animal and now has quite lost his sensitiveness. This patient is a hostler, who was formerly described as being able to go back to work in the stable. The laboratory boy who was sensitive to guinea-pigs and who was reported as being able to tolerate these animals cannot be traced. Six patients pronounced themselves free from trouble, but unfortunately they did not say whether or not contact with animals occurs in their daily life, and so while their cure is certain in the clinical sense, it is not so certain in the immunologic sense. Ten other patients are also free from asthma, but they are only too well aware of their sensitiveness, and their freedom from asthma is due only to the great pains which they take to avoid possible contact with animals. Clinically, all of these patients are "cured." The "prize patient" (Agnes C.), who was treated successfully with horse dander extract in 1919, is now well and most of the time can tolerate the presence of animals without difficulty; however, if she happens to have a cold in the head at the time of exposure, wheezing does occur. Another patient (G.) should be noted. He was entirely free from asthma after his dog was disposed of in 1925, but last summer he had whooping cough and some asthma followed this disease, although no evident exposure to animals was observed at the time. The attack was short, and he is now well again. Mary G., a girl of 15, with a typical sensitiveness to horses, was given specific treatment with horse dander extract in 1920, with some success. Later she became a nurse, and was free from asthma for several years. Unfortunately, she contracted acute bacterial endocarditis and died. This leaves only 1 patient (S.) in whom the results are not still good. When first seen, this patient had foci of infection in her sinuses, tonsils and teeth, and while some of the conditions were treated, it is quite likely that more trouble has developed lately and thus accounts in part for the return of her asthma, which now comes at all seasons of the year in attacks which are usually precipitated by colds in the head.

The group of patients with infections with animal asthma should be mentioned only to point out that in the two year follow-up, none of the patients were "cured."

Extrinsic Mixed and Unidentified Cases.—This was the title formerly given to a comparatively large group of patients whose asthma bore a definite relation to changes in the environment, but in whom it was not possible to identify the precise substance to which they were sensitive. In most of these cases there was more than one plausible

explanation for the good result. Many of these patients had positive skin reactions to such substances as house dust, mattress hair, feathers and sometimes animal danders and pollens. In the former paper, the whole group was divided into 2 sections, according to the presence or absence of positive skin tests.

Of the 22 patients whose tests were positive and who were "cured," 11 reported that they are still free from asthma, and none of these 11 even suggested that they tend to wheeze when in certain places. On the other hand, there is another group of 7 patients who are essentially well, but nevertheless recognize that they cannot go to certain houses without having a new attack of asthma. Three of them still have hay fever in the ragweed season, although this ragweed was never the sole cause of their trouble. Four of the 7 said that when they have a heavy cold, they are likely to wheeze a little. The question of foci of infection is of interest. In 4 of the 11 favorable cases the patients originally had some evidence of sinus disease, and 2 others had infected tonsils, but none of them had undergone an operation. Among the 7 who are still subject to mild attacks, 2 formerly had some thickening of the sinus membrane.

Four patients of the original group have not been heard from, and 1 of them had a large mucous cyst in the right antrum and a thick membrane in the left antrum, but so far as is known, no operation was performed.

The patients with mixed extrinsic causes who had negative tests are in every way analogous to those in the preceding group. Of the 18 patients originally "cured," 10 reported themselves as still entirely free from asthma. Some of them had moved, but others made no mention of their environment. Of the 8 others, 1 has not been heard from, pulmonary tuberculosis developed in 1, but with no asthma in the interim, while another was in rather poor health because of a renal infection, which required operation. Her asthma appeared again during the beginning of the infection but since the operation, three years ago, it has disappeared. Four patients admitted that they have attacks of asthma when they have a bad cold. One patient had a relapse, and is now as bad or worse than in the beginning. This woman had formerly reported herself as entirely free from trouble for four years after the time of her marriage and a change of residence, except that at the end of three years she went back to her mother's house and had asthma during the visit. Now she has three small children and has to work hard. She has lost a good deal of weight, and severe attacks of asthma have again occurred. Quite likely, the attacks are due to a new hypersensitiveness which she has developed to some substance, perhaps a piece of furniture or other material, in her environment. Foci of infection in the nose and throat were found in 6 of the original 18 cases. No opera-

tions were performed. Three of these patients are now in the group of those perfectly well, the other 3 still being subject to asthma.

Extrinsic Specials.—The group formerly so designated contained 17 patients with interesting cases. Eleven of them were sensitive to foods. One has not been heard from. Five have completely recovered, not only in the clinical but also in the immunologic sense, since they can now eat the offending foods without trouble. Four children are of special interest. Two of them are still sensitive to fish and eggs and have been careful to avoid these foods for the past ten years. One of them, Robert L., now aged 12, has had slight asthma in September for the past three years (his ragweed test was negative in 1921) while Constance H., now aged 20, has "no asthma as a general rule but if I get tired and at the same time have a cold, it usually develops into a light attack of asthma.—Dust aggravates."

John T., who at the age of 5, in 1921, was hypersensitive to wheat and eggs and was relieved by a test-negative diet, now, at 15, eats everything. He wrote, "Rabbits are the only things that bother me." The boy with hypopituitarism, who was sensitive to nuts, still avoids nuts, but he observed that "Horses and cats still bother me." The skin test to horse dander was positive eight years ago, but did not appear to be of clinical importance at that time. Apparently in each of these 4 children a hypersensitiveness to other substances has developed.

One patient has asthma again in severe form. Mrs. L., aged 40, was relieved of her asthma for seven years after following a diet limited to the test-negative substances as found. In 1927, she described herself as "one of the seven wonders of the World." In July, 1931, she wrote that the sinuses were infected and that for the past eight months she had had asthma in severe form.

There are 6 patients sensitive to dust. Two reported themselves as well, without making further comment. A third is well, but continues to avoid feathers. A fourth went to California in 1926, and recovered from his asthma. His letter dated March, 1932, is interesting. It contains this note: "I had my nose operated on for polypus—other than that, no trouble." The fifth and sixth patients were young girls whose asthma was due to a hypersensitiveness to feathers. Now, seven and five years later, their letters do no mention feathers or asthma, but typical ragweed hay fever has developed in Mrs. W., while Barbara H. has urticaria. It would be interesting to know whether a sensitiveness to some food had developed in the latter patient.

Taking the food and dust cases together, there are 11 patients who are still free from asthma, and all of the others except Mrs. L. are much improved, but it is only too evident that in most of the cases the "cure" is merely a clinical and relative change. Several patients are no longer troubled by the original substance, but they and others neverthe-

less demonstrate their allergy by their capacity to develop sensitiveness to still other materials.

Foci of infection were not found in this special group, except in 1 case in which there was frank evidence of sinusitis with polypi. This is the patient who recovered while in California and who had recently had a polypus removed, without further asthma. The patients with extrinsic cases in general are far from "cured." The figures show that 31 of the 102 patients with two year "cures" have had relapses, and many of those who are listed as "still cured" depend for their freedom on the careful avoidance of the specific substance. Several interesting points will be discussed later.

INTRINSIC ASTHMA

Bacterial Asthma.—The final end-results among patients with so-called bacterial asthma are comparatively satisfactory. The 59 "cured" patients are divided into 25 adults and 34 children. Among the 25 adults, 3 are dead of other causes, and 3 have not been heard from, but 6 have remained free from trouble since the last follow-up four years ago. Only 3 patients have had asthma in the meantime. One of the 3 is an athletic women, now 33 years old, who was first seen at the age of 19 on account of asthma which had lasted for one year. At that time she was "cured" after taking benzyl benzoate; her case was described in 1928. For thirteen years she has had no asthma at all, and, in the meantime, she has married and borne two children. Within a year, however, asthma developed, which came on particularly after she played a violent game of squash rackets. On several occasions, the attacks so induced persisted for the following twenty-four hours. There was nothing new about her play for she had been interested in squash rackets for years. The second patient who had a relapse was likewise athletic and as a child had asthma only in association with her sports, particularly tennis. The reason for her improvement was not clear, but the fact is that she did well for about eight years until her marriage. After that event, asthma occurred when the first child was born and reappeared during the second pregnancy. With the third pregnancy, she had asthma once more, having been entirely free since the birth of the second child. The third poor result was also in a woman, who was seen in 1924 at the age of 30. At that time she was given 5 doses of vaccine and thereafter had no further asthma, although she was living at the same address, until the fall of 1930, six years later, when another attack followed a bad cold. Since then, she had been miserable with asthma, which occurred at all seasons of the year and without apparent cause.

Only 1 patient among these 25 had evidence of sinusitis, and she is now free from asthma.

The children, like the adults, have done well. Twenty-three of the total 34 said that they had been free from asthma for the past four years, or since the last note, which often represents a much longer total period.

However, they have not all done well. Four of the children have not been heard from. Five others have occasional spasmodic attacks which are never severe. In 3 of the 5, these attacks occur only during the early autumn, and likely a sensitiveness to ragweed has developed, although the skin tests, which ten years ago showed no reaction to any of the common substances, including the pollens, have not been repeated. In the other 2, mild attacks have occurred within the past year following colds, the relapses having come after free periods of seven and nine years, respectively. Two patients seem to have had real relapses, in that after a free period, which lasted for only two years, their asthma again occurs at frequent intervals and is sometimes of considerable severity. The history however, does not suggest the probable cause. Neither of these 2 patients had foci of infection when first examined.

Reflex Asthma.—This term was used to define the cases of those patients whose troubles depended on some definite lesion, usually an infectious process elsewhere than in the lung itself. The whole group of 28 cases has been subdivided according to whether the source of trouble was outside the respiratory tract or inside of it, in the tonsils or in the paranasal sinuses. In the group described originally as having asthma dependent on a lesion outside of the respiratory tract, there were 18 patients designated as "cured." Of this number, 9 are still free from asthma four years later. Four still date the time of "cure" from the operation, which in 2 cases was the removal of gallstones; in 1, the extraction of abscessed teeth, and in the fourth (a child), tonsillectomy and appendectomy. Three other patients attributed their improvement to better digestion following the changes in diet which were advised ten years ago. The 9 cases also include 2 former children who are still free from trouble. In these 2 cases, however, the original asthma was never severe and occurred only in slight attacks following colds in children who were thin, frail and in a poor general condition.

Four patients in this reflex group are not "cured," though their asthma is not so troublesome as before. Two patients still show a tendency to wheeze in the winter whenever they catch cold. A man of 45, whose teeth were removed in 1923, gained weight up to 200 pounds (90.7 Kg.); he said that he now wheezes on exertion in the winter. A woman, whose appendix, teeth and tonsils had been removed and who was apparently relieved permanently at a later date by vaccines, suffered a return of her asthma; she wrote that a physician wants to operate on her nose and throat. It is unfortunate that 5

patients in this group have not been heard from, especially as all of them did so well at first after the removal of their abscessed teeth or infected tonsils.

Diseases of the paransal sinuses appear to be responsible for the asthma in 10 of the original "cured" "reflex" cases. The operations were on the tonsils in some cases, and on the sinuses in others. One patient cannot be traced. Two children and 1 adult have remained well for more than nine years following tonsillectomy. Marjorie T., aged 12, who had had asthma for three years, was found in 1921 to have badly infected tonsils and many polypi in both nares. Both antrums were dark. At operation, the tonsils and many polypi were removed. Other polypi were taken out from time to time during the next three years, but since 1924 she has had no further asthma; this good result is in spite of the fact that polypi have occasionally formed and been removed. Kenneth B., a poorly nourished, tired, pale boy of 6 with persistent asthma of some severity had infected tonsils which were taken out at the age of 7. He is now 15 years of age, weighs 188 pounds (85.3 Kg.) and is 6 feet tall (182.9 cm.). There are at least 3 patients who have had operations on the sinuses with good results which appear to be permanent. Mrs. D., a woman of 63, who had had asthma since the age of 60, had her ethmoids and antrums operated on, and in the nine years since then she has had no asthma, although she is living in the same place. Mrs. W., aged 43, who had asthma for eight years and polypoid ethmoiditis, has been entirely well for eight years since an operation. Mrs. R., aged 54, has a similar history. On the other hand, Mrs. R., aged 55, whose sinuses were operated on in 1921, caught a severe cold in 1930, and since then has had occasional slight attacks of asthma, which fortunately are never severe. Much the same story applies to 2 other patients who are infinitely better, but who still may have asthma with colds or with sudden changes in temperature. One patient has been lost from observation.

Cardiac Asthma and Chronic Bronchitis with Emphysema.—These conditions have poor prognoses, as is shown by the practical absence of "cured" cases in the series of 1928. At that time, too, the diagnosis of cardiac asthma was based on even less definite evidence than now. Today, two important points in the diagnosis of cardiac asthma are recognized: (1) the age of onset is past 50, and (2) the attacks are precipitated by exertion or excitement. In a patient, aged 65, who had had severe asthma since the age of 17, symptoms of decompensation and angina pectoris subsequently developed. Today her heart disease would be regarded as something independent of her asthma, and she would not be described as having cardiac asthma. She died at the age of 71 of angina pectoris; she had no real wheeze for the past ten years.

Three patients were formerly described as "cured" despite their chronic bronchitis and emphysema. Two of them were women who did well for two and five years, respectively, up to 1928, after taking potassium iodide. The younger patient, aged 53, has continued well to the present time, or for a total of six years, while the older one, aged 61, died suddenly after a free period of eight years. The Jewish tailor is "lost."

Unclassified Asthma.—This heading is necessary. Of 15 patients "cured" in 1928, 12 are still free from trouble, though 1 of the 12 has nasal polypi which must be removed about once each year. One patient who was supposedly "cured" by intravenous doses of sodium iodide did well for only two years and now is ill again. The remaining 2 patients cannot be traced.

COMMENT

The results of this study show that the longer a series of patients with asthma is studied, the more evident it becomes that true "cure" is a doubtful prospect even though many patients remain symptom-free for long periods. The number of "cured" cases, which was 213 in 1928, has been reduced to 131, or 12 per cent, of the original total of 1,074 cases. The dictum "once an asthmatic, a patient is usually a potential asthmatic for the rest of his life," as pronounced by Vander Veer,[2] seems to be borne out by these findings.

Why is treatment so difficult? Why are the results so poor? As said four years ago, the results in the extrinsic group show that cure has been accomplished by removal of the trigger which fired the attack, but obviously the gun remains loaded in most, and probably in all, cases. Evidently fundamental allergy is a remarkably persistent trait. The conception of the "capacity to develop sensitiveness" as a supplement to von Pirquet's conception a "capacity to react" (*Reactionsfähigkeit*) seems justified by the observation of patients over periods long enough to see that they tend to develop sensitiveness to new substances in their environment. It is the capacity which is fundamental. Its nature is quite unknown.

The influence of a chronic sinus infection is always interesting and difficult to analyze. Whether more patients with sinusitis have asthma than do not have asthma is uncertain, but it is evident that sinusitis is a common finding in asthma. Acute colds and acute sinus infections can cause asthma in short attacks, which last for the duration of the infection. Furthermore, chronic sinus infections can cause asthma, which then is also chronic, and in a few cases, the chronic asthma is relieved for long periods by operations on the sinuses. In these cases, the sinusitis appears to be the primary exciting cause of the asthma.

2. Vander Veer, A., Jr.: The Present Status of the Treatment of Hay Fever and Asthma, Am. J. M. Sc. **164**:97, 1922.

In other cases, however, such good results have not followed radical treatment, and in still others, clinical recovery has occurred even though nasal polypi and other evidences of sinus infection were still present.

Finally, there are cases in which the sinus lesion is a complication which adds to the primary cause to produce a summation or total which in turn leads to asthma. In these cases, neither the extrinsic factor alone nor the infection alone is sufficient to produce symptoms which depend on the presence of infection at the time of exposure to the foreign substance.

Can the high incidence of sinusitis be correlated with the capacity to develop sensitiveness? Is it possible that allergic tissue reactions tend to hold the infection while immune serum reactions tend to destroy it? The thought is attractive. So far one can only speculate on it. Progress will be more rapid as one learns that in asthma the fundamental problem lies not in the sensitiveness to any particular protein or in the incidence and treatment of nasal disease, but in the study of the capacity to develop sensitiveness to foreign substances. Doubtless this capacity is inherited and may well be, as Morris H. Kahn [3] suggested, "rooted in the biologic and physico-chemical structure of the chromosomes."

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3. Kahn, M. H.: The Present Status of Curability of Bronchial Asthma, Arch. Int. Med. **39**:621 (May) 1927.

HYPERPROTEINEMIA DUE TO BENCE-JONES PROTEIN IN MYELOMATOSIS

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Elevation of the serum protein content, except in dehydration, is observed rarely in clinical practice. Even with marked loss of fluid from the body the increase of protein in the blood usually is not great. True hyperproteinemia is exceedingly rare. Loeper, Forestier and Tonnet [1] found the serum protein to be 11 mg. per hundred cubic centimeters in one case of malignant tumor of the kidney. Wu [2] reported that one patient with kala-azar had a serum protein of 10.52 mg. and a serum globulin of 9.06 mg. The highest serum protein content observed by Rowe [3] was 10.4 mg. in a patient suffering from glandular enlargement. However, no known clinical syndrome shows constantly an increase in the protein of the blood.

Few studies on proteins of the blood in patients with multiple myelomas have been reported. Ellinger [4] demonstrated qualitatively the presence of Bence-Jones protein in blood and in ascitic fluid, as did Askanazy [5] in blood and in pericardial and pleural fluid; Weber [6] found it in pericardial fluid, and Hewitt [7] in the blood of patients suffering from multiple myelomas. In 1917, Jacobson [8] found and determined quantitatively a

From the Cleveland Clinic.

1. Loeper, M.; Forestier, J., and Tonnet, J.: Chemistry of the Blood in Cancer, Presse méd. **29**:333, 1921.

2. Wu, H.: New Colorimetric Method for Determination of Plasma Proteins, J. Biol. Chem. **51**:33, 1922.

3. Rowe, A. H.: The Albumin and Globulin Content of Human Blood Serum, Arch. Int. Med. **18**:455 (Oct.) 1916.

4. Ellinger, A.: Das Vorkommen das Bence-Jonesschen Körpers im Harn bei Tumoren des Knochenmarks und seine diagnostische Bedeutung, Deutsches Arch. f. klin. Med. **62**:255, 1899.

5. Askanazy, S.: Ueber die diagnostische Bedeutung der Ausscheidung Bence-Jonesschen Körpers durch den Harn, Deutsches Arch. f. klin. Med. **68**:34, 1900.

6. Weber, F. P.: Multiple Myelomatosis with Bence-Jones Protein in the Urine, Am. J. M. Sc. **126**:644, 1903.

7. Hewitt, L. F.: Bence-Jones Proteins, Biochem. J. **23**:1147, 1929.

8. Jacobson, V. C.: A Case of Multiple Myelomata with Chronic Nephritis Showing Bence-Jones Protein in Urine and Blood Serum, J. Urol. **1**:167, 1917.

large amount of Bence-Jones protein in the blood of a patient suffering from myelomatosis and severe chronic nephritis. The total content of protein in the serum of this patient was not determined, but evidently was high, since the value for the Bence-Jones protein alone was 7.87 mg. per hundrded cubic centimeters. Jacobson noted precipitation of the protein on inactivating (by heating for one-half hour at 56 C.) the serum in preparation for a Wassermann test. This phenomenon was observed by Short and Crawford [9] also.

Recently Perlzweig, Delrue and Geschickter [10] reported a single case of myelomatosis in which the total protein in the plasma amounted to 13.84 mg. per hundred cubic centimeters. They precipitated a fraction of the protein from this serum by heating to 56 C., but this remained insoluble at the boiling point. These authors concluded that only a small amount of Bence-Jones protein was present in the blood serum of their patient, and that the high value for protein was due to a physiologic reaction in response to the introduction of this small amount of foreign protein. Hewitt [7] called attention to the fact that different samples of Bence-Jones protein vary greatly in solubility and in other physical and chemical properties. Hopkins and Savoy [11] found that this variation in solubility is dependent on the acidity and the salt content. To us, it seems more than probable that the increase in total serum protein in the case reported by Perlzweig, Delrue and Geschickter was due to the presence of Bence-Jones protein. Since there are no cases reported in the literature on hyperproteinemia proved to be due to Bence-Jones protein, it seems worth while to report two such cases that we have had under observation recently.

In the first case, in view of the high amount of total protein in the blood serum and the report of precipitation of the blood serum during inactivation for the Wassermann test, special studies of the serum for Bence-Jones protein were made. Several times, large amounts of a protein precipitating at 56 C. and almost completely dissolving at the boiling point were demonstrated, and quantitative estimations were made. Two procedures were used in analyzing this protein quantitatively. The undiluted serum, the protein content of which had been determined, was heated in a water bath at 56 C. In half an hour cold distilled water was added; the mixture was centrifugated, and the washings were saved. The precipitate was washed several times in this

9. Short, J. J., and Crawford, J. R.: Bence-Jones Protein in Blood Serum Leading to Detection of Multiple Myelomatosis: Report of a Case, J. Lab. & Clin. Med. **14**:1092, 1929.

10. Perlzweig, W. A.; Delrue, G., and Geschickter, C.: Hyperproteinemia Associated with Multiple Myelomas, J. A. M. A. **90**:755 (March 10) 1929.

11. Hopkins, E. G., and Savoy, H.: A Study of Bence-Jones Protein and of the Metabolism in Three Cases of Bence-Jones Proteinuria, J. Physiol. **42**:189, 1911.

manner. The total protein in the washings was determined, and the amount of protein precipitated was calculated by subtracting the total protein in the washings from the total protein of the original serum. The precipitated protein also was suspended in distilled water and was determined quantitatively. The amounts of Bence-Jones protein as determined by these two methods corresponded closely. Hence we feel that the values obtained must be approximately correct.

Perlzweig, Delrue and Geschickter suggested that Jacobson's findings might be explained on the basis of precipitation of a large amount of euglobulin at 56 C., with the occlusion of a small amount of Bence-Jones protein in the precipitate. This explanation certainly is not correct in our cases, since the precipitate was almost completely soluble at the boiling point; this would not be possible if the major part of it were globulin, although it is possible that in our experiments a small amount of globulin was carried down with the precipitation of Bence-Jones protein. Control studies with the same technic on normal serums gave no precipitate. In the cases reported here, most of the Bence-Jones protein came down in the euglobulin fraction on fractional precipitation with sodium sulphate. This is what might be expected, since the close relation of Bence-Jones protein to globulin has been emphasized in the careful chemical and physical study made by Hopkins and Savory.[11] Many of the properties of a solution of Bence-Jones protein at the boiling point and of typical blood globulin at room temperature are identical. Hopkins and Savory concluded: "The fundamental difference between Bence-Jones protein and globulin is the difference of temperature factor involved in their equilibrium with salts. What is special in the temperature relation is the basis of what is special in the physical chemistry of the Bence-Jones protein."

REPORT OF CASES

CASE 1.—A white man, 64 years of age, was first seen in the Cleveland Clinic on June 23, 1931. He complained of stiffness in the neck which had been present for three months. Two weeks before he consulted us, while playing golf, he had begun to have pain in the lower part of the back which confined him to bed. It was a dull pain radiating anteriorly around to the abdominal muscles and was relieved considerably by the application of heat. The patient's clinical history previous to the onset of these symptoms seemed irrelevant; however, at times he had felt some stiffness and pain in various joints and muscles.

General physical examination showed no significant findings except for definite limitation of abduction and rotation in the left shoulder and of extension in both knees. The lumbar spine was flat, and there was spasm of the lumbar muscles. The patient had great difficulty in rising from the prone position.

Examination of the blood revealed marked anemia. The erythrocytes numbered 3,240,000 and the leukocytes 5,400. The urine had a low specific gravity, a slight trace of albumin and hyaline and granular casts. The Wassermann test of the blood could not be made, because a precipitate was formed in the serum during inactivation (56 C.).

Roentgen examination of the lumbar spine showed marked generalized atrophy of the spine and lipping of the vertebrae. The patient was put to bed and physical therapy was instituted, but he became progressively worse. Even with rest in bed the severe pain with movement persisted. At times the pain in the chest and in the lower part of the lumbar area was extremely intense.

On account of continued pain the patient was admitted to the Cleveland Clinic Hospital on Oct. 10, 1931. Further studies at that time revealed the correct diagnosis of myelomatosis. The clinical course was steadily downward. The anemia became more pronounced, and the pain accompanying movement increased. Roentgen examination of the spine showed compression of the tenth dorsal vertebra. This was considered by the roentgenologist to be due in all probability to metastatic malignancy. The generalized atrophy of the bones was striking, but no discrete multiple punched-out areas typical of myeloma were found. The long bones were not involved. The urine was examined repeatedly, but no Bence-Jones bodies were found. No primary malignant tumor was revealed, although a careful clinical search was made. A biopsy of the twelfth rib was made, but the only finding of significance was hyperplasia of the bone marrow. Later spontaneous fracture of several ribs occurred when the patient was moved in bed. The anemia

TABLE 1.—*Results of Chemical Examination of the Blood (Case 1)*

Date, 1931	Nonprotein Nitrogen, Mg.	Urea, Mg.	Creatinine, Mg.	Uric Acid, Mg.	Calcium, Mg.	Phosphorus, Mg.	Chloride, Mg.
Oct. 13	36.4	...	...	4.8	14.0	4.01	...
Oct. 28	....	...	...	...	13.5	4.57	...
Nov. 1	....	...	...	...	13.2	4.60	...
Nov. 7	....	45	1.4	4.6	15.5	2.60	544
Nov. 21	....	81	...	...	....	....	...
Nov. 25	....	210	...	...	12.2	8.00	544

continued to increase, and bilateral pleural effusion and terminal bronchopneumonia developed. This caused the patient's death on Nov. 25, 1931, five months after his first admission to the clinic.

All the bones examined at necropsy showed marked loss of calcium salts, thinning of the cortex and atrophy of the trabeculae. The cortex of the vertebrae was especially thin. The marrow spaces as well as the entire body of the vertebrae were filled with soft, friable, very cellular material. Only in the twelfth dorsal vertebra was a circumscribed area of infiltration found; this was filled with white, soft, cellular material. There was no myelomatous or other neoplastic infiltration of the periosteum or surrounding tissues in any of the bones examined. Stained smears from the marrow showed microscopically a predominance of large cells simulating plasma cells. The bone marrow in the ribs and manubrium was hyperplastic.

Specimens of blood from the heart, of spinal fluid and of pericardial and pleural fluids were obtained at autopsy for chemical study. The clinical diagnosis was myelomatosis, although the roentgenographic findings were not typical and no Bence-Jones bodies could be demonstrated in the urine.

The first chemical examination of the blood was made on Oct. 10, 1931, the day of the patient's admission to the hospital. The value for nonprotein nitrogen was normal (36.4 mg.); that for uric acid was elevated (4.8 mg.); that for phosphorus was above normal (4.01 mg.), and that for calcium was very high (14 mg.). The amount of urea in the blood gradually rose, reaching 210 mg. per hundred cubic centimeters before the patient's death. The level of calcium in the

blood was constantly high, varying from 12 to 15.5 mg. At the time of the patient's death the phosphorus measured 8 mg. (table 1).

A specimen of spinal fluid obtained on Nov. 10, 1931, showed 2.9 mg. of protein and 5.8 mg. of calcium per hundred cubic centimeters. No Bence-Jones bodies could be demonstrated in this specimen or in a second specimen obtained at necropsy. The result of the dextrose tolerance test was normal.

The protein content of the serum was determined repeatedly and constantly found to be high. The elevated protein content was due entirely to an increase in the globulin portion. The increase in the globulin might be accounted for by the presence of Bence-Jones protein. The highest value for total protein was 13.78 mg. per hundred cubic centimeters, and the lowest was 10.06 mg. The globulin portion varied from 6.53 to 11.34 mg. The Bence-Jones protein in the blood varied from 7 to 9 mg. At autopsy, the pleural fluid contained 3.4 mg. and the pericardial fluid 2.5 mg. of Bence-Jones protein. The results of the studies of protein are shown in table 2.

In view of the increased calcium in the blood the possibility of hyperparathyroidism was considered. The amount of phosphatase in the plasma, determined

TABLE 2.—*Estimations of Protein (Case 1)*

Specimen	Date, 1931	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	Bence-Jones Protein, per Cent
Blood	Oct. 13	12.25	2.99	9.26	....
	Nov. 1	10.94	2.70	8.24	....
	Nov. 7	13.78	2.44	11.34	....
	Nov. 16	11.93	2.55	9.38	8.75
	Nov. 17	10.47	1.25	9.22	7.85
	Nov. 21	10.72	3.25	7.47	7.85
	Nov. 25	10.06	3.53	6.53	....
	Autopsy	10.40	....	....	7.40
Pericardial fluid	Autopsy	5.40	....	....	2.60
Right pleural fluid	Autopsy	8.50	....	....	5.10

according to the method of Kay, was normal (0.12 units per hundred cubic centimeters).

CASE 2.—A white woman, 49 years of age, was seen first in the clinic on July 29, 1931; she was complaining of pain in the lower part of the lumbar region and of weakness in the legs. She stated that she had been well until November, 1930; later she began to have a dull pain in the right flank which remained localized and was never severe. At that time she was studied at another hospital, where a diagnosis of enlarged kidney was made. Later the pain became localized in the upper part of the right lumbar region and was aggravated by any movement. The weakness in the legs had been progressive and had necessitated the use of a cane and crutches. She stated that her physicians had observed albuminuria for some time. She had lost 25 pounds (11.3 Kg.) in weight since the onset of the illness.

On general physical examination the patient's temperature and pulse rate were normal; she weighed 145 pounds (65.8 Kg.), and her blood pressure was 135 systolic and 80 diastolic. Examination of the heart and lungs revealed no abnormality. The abdominal muscles were tense. There was practically no motion in the spine. There were marked scoliosis and tenderness on pressure over the spine in the lumbar region and the lower part of the thoracic region. Voluntary movements of the muscles, especially of the legs, were weak.

Roentgen examination showed widespread destructive tumors typical of multiple myeloma in the vertebrae, in the ribs, and in the shoulder and hip girdles. The

eleventh dorsal and the first and fifth lumbar vertebrae were compressed. The skull and long bones also showed areas of destruction due to multiple small tumors.

The specific gravity of the urine varied from 0.012 to 1.020. Albumin in varying amounts was constantly present. Bence-Jones protein was detected in the urine at every examination. One quantitative determination of Bence-Jones bodies showed the amount to be 0.56 mg. per hundred cubic centimeters. Marked anemia was present. The erythrocyte count was 2,840,000; the leukocytes numbered 5,400, with a normal differential count, and the amount of hemoglobin was 58 per cent (9 Gm.). The blood sugar was found to be 87 mg. per hundred cubic centimeters; the urea, 24 mg.; the chlorides, 594 mg.; the calcium, 11.15 mg., and the phosphorus, 4.28 mg. The spinal fluid contained 110 mg. of protein per hundred cubic centimeters, but no Bence-Jones bodies could be demonstrated. A precipitate was formed in the serum during the process of inactivation for the Wassermann reaction.

The first estimation of protein in the blood showed the total amount to be 11.37 mg. per hundred cubic centimeters, of which 2.44 mg. was albumin and 8.93 mg. globulin. A later complete study of the protein revealed the following: total protein, 10.02 mg.; albumin, 2.30 mg.; globulin (total), 7.72 mg.; euglobulin, 6.32 mg.; pseudoglobulin I, 0.66 mg.; pseudoglobulin II, 0.74 mg., and Bence-Jones protein, 4.13 mg. The important chemical findings in the blood are summarized in table 3. The patient's condition did not change during her stay of ten days in the hospital.

TABLE 3.—*Results of Chemical Examination of the Blood (Case 2)*

Date	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Serum Protein, per Cent						
			Total	Albumin	Globulin	Euglobulin	Pseudoglobulin I	Pseudoglobulin II	Bence-Jones Protein
7/29/31	11.15	4.28	11.37	2.44	8.93	....	....	....	....
7/30/31	.....	....	10.02	2.30	7.72	6.32	0.66	0.74	4.13

COMMENT

In these two cases the amount of total protein was high, and the increase was proved to be due to the presence of a large amount of Bence-Jones protein. In each instance there was a precipitation of the foreign protein on inactivation of the serum for the Wassermann test. In the Cleveland Clinic other cases of multiple myeloma have been studied without the finding of hyperproteinemia or Bence-Jones bodies in the serum. No logical explanation for the occasional finding of Bence-Jones protein in the blood is apparent. Jacobson thought that a complicating nephritis, preventing excretion, was responsible for the Bence-Jones proteinemia and the absence of the protein in the urine of his patient. In the two cases reported here there was no evidence of disease of the kidneys to explain the hyperproteinemia. Aside from its diagnostic value, the presence of Bence-Jones bodies has no clinical significance so far as is known. Owing to the protein content, the osmotic pressure of the serum is increased somewhat, but not greatly,

since the osmotic pressure exerted by globulin is only one-fourth as great as that of albumin.

The blood calcium was high in both of our cases. In case 1 there was evidently a widespread loss of calcium salts from the bones. In case 2 only focal areas of bone destruction were present. The increase of calcium in the blood is easily explained on the basis of the decalcification incident to the widespread osseous lesions of the disease.

SUMMARY

Two cases of myelomatosis with a high content of protein in the blood serum are reported.

The increase in protein was in the euglobulin portion of the globulin.

Bence-Jones protein in large amounts was demonstrated in the serum of both patients.

The increase in the total protein in the blood was proved to be due to the presence of large amounts of Bence-Jones protein.

A high level of calcium was found in the blood of both patients; in one, the roentgenograms showed only a generalized atrophy of bone; in the other, there were the characteristic punched-out areas of bone destruction.

MATURING EFFECT OF ROENTGEN RAYS ON BLOOD-FORMING CELLS

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There are numerous views as to the nature of the action of roentgen rays on living tissues. In general, it is felt that small doses "stimulate" and large doses "depress." After the therapeutic use of large doses, death or a decrease in the size of the exposed tissue follows. Whether this action is one of a toxic necrosis of tissue directly, a mechanism disturbing the cell division or an increase in the rate and intensity of the normal processes in the life of the cell is a matter of discussion.

For the study of the effect of roentgen rays on living tissue, the blood offers admirable material. The polymorphonuclear leukocytes may be recognized morphologically in twelve or more stages in the course of their life history, and at least five or six definite stages in the maturation of a red blood cell can be identified. This enables one to study the effect of irradiation with relation to the rate of maturation, so that it can be noted whether the cells reach maturity and die of senility, or whether there is a toxic necrosis, with death in the stage during which the cell was irradiated.

The material for study consisted of patients with various types of leukemia, lymphoblastoma or cancer, the data obtained representing observations on over 923 patients. Studies of the blood were made before and after treatment over long periods, occasionally with many observations at short intervals.

Of the cells that grow in the bone marrow, the youngest stage seen in the blood under pathologic conditions is that of the primitive myeloblast. In the bone marrow this is a small cell, which is slightly larger than a red blood cell, and which resembles a lymphocyte in certain superficial aspects. This cell normally grows larger and becomes a myeloblast. The next stage is that of the myelocyte, the largest cell of the series. The myelocyte shrinks and forms the metamyelocyte, and, as the shrinking process continues, the nucleus becomes indented; finally, distinct lobes appear, and the cell becomes a polymorphonuclear leukocyte. The

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myeloblasts and the primitive myeloblasts have the power to divide and produce new myeloblasts or to mature and produce adult polymorphonuclear leukocytes. When a cell of the bone marrow is stimulated, it does one of two things: It may divide and reproduce rapidly (myeloblasts and primitive myeloblasts), or it may run through the rest of the stages of maturation and become an adult cell. When a person is exposed to roentgen rays, the myeloblasts reproduce more myeloblasts (an undesirable effect) and the myelocytes mature to polymorphonuclear leukocytes (a desirable effect).[1] This is readily seen when careful studies on the blood are made at frequent intervals before and after roentgen treatment.

A similar maturation process takes place in the red blood cells. The youngest red cell is a nucleated form, normally confined to the bone marrow. This matures into the reticulocyte, then into the granule and then into the mature erythrocyte. Immediately (less than one-half hour) after adequate roentgen therapy, the number of granular red blood cells increases, showing that reticulocytes have been matured to the next older stage. Then the reticulocytes increase, showing that the nucleated cells have been stimulated to mature quickly to the reticulocytic stage. As days pass the reticulocytes decrease in number and mature into the granule stage, and the number of these cells again rises. Then the number of mature cells increases.[2] This observation is well shown by a study of patients with cancer, leukemia and lymphoblastoma, as well as by the ability of roentgen irradiation (Minot and Lee,[3] and others[4]) to induce a remission in pernicious anemia or improvement in other types of anemia. Pernicious anemia is characterized by gross immaturity of the red blood cells in the bone marrow, and the stimulus of the roentgen ray makes the cells mature.

Similar evidence may be gathered from a study of the lymphocytes. The youngest stage reaching the peripheral circulation under pathologic conditions is the primitive lymphoblast, which closely resembles the

1. Isaacs, R.: Blood Changes in the Leukemias and Lymphomata and Their Bearing on Roentgen Therapy, Am. J. Roentgenol. **24**:648, 1930.

2. Isaacs, R.: Effect of Roentgen Ray Irradiation on Red Blood Cell Production in Cancer and Leukemia, Am. J. M. Sc. **171**:20, 1926.

3. Minot, G. R., and Lee, R. I.: Treatment of Pernicious Anemia, Especially by Transfusion and Splenectomy, Boston M. & S. J. **177**:761, 1917.

4. Bucky, G., and Guggenheimer, H.: Steigerung der Knochenmarksfunktion durch Röntgenreizdosen, Klin. Wchnschr. **1**:11, 1922. Dazzi, A.: Morphological Changes of the Blood, Following Irradiation of the Splenic Area, with So-Called Stimulating Doses, Radiol. med. **11**:529, 1924. Faberi, M.: A Case of Severe Anemia of Aplastic Type Treated with Radiotherapy, Policlinico (sez. prat.) **31**: 1229, 1924. Tomanek, F.: Results of Radium Treatment of Pernicious Anemia, Časop. lék. česk. **63**:549, 1924. Yousenburg, A.: Roentgen Therapy in Blood Diseases, Vestnik rentgen. i radiol. **3**:18, 1924.

primitive myeloblast in its appearance and its behavior to roentgen irradiation. The cell normally is confined to the lymphoid tissue and matures thus: into the lymphoblast, the large lymphocyte, the medium-sized small lymphocyte and, finally, into the adult small lymphocyte. Exposure to roentgen radiation during the primitive lymphoblastic and the lymphoblastic stages causes the cells to reproduce with the rapid production of additional primitive lymphoblasts. As the bulk of the cells are in this stage in acute lymphatic leukemia and in the terminal stage of chronic lymphatic leukemia, roentgen irradiation does not lower the white blood cell count appreciably, and frequently aggravates the condition. When the bulk of the cells are lymphocytes of medium or small size, roentgen irradiation stimulates them to grow old, and they are excreted into the gastro-intestinal tract (Isaacs and Danielian,[5] Bunting and Huston[6]). Therefore, the quickest response in the reduction of the white cell count after adequate therapy occurs when the bulk of the cells are lymphocytes of small and medium size (that is, relatively mature), and the response is but slight when the bulk of the cells are large lymphocytes and lymphoblasts. The stimulation of young cells to grow older results in an initial increase in the number of lymphocytes in the blood stream before the decrease starts. This is best seen when small doses of radiation have been used.[7]

The monocytes, especially those seen in monocytic leukemia, go through a similar process of stimulation and development, although at a much slower rate.

While it has generally been considered that "small doses stimulate and large doses depress," in reality, all doses are stimulating; the larger doses, however, cause such a rapid rate of growth that the normal end is soon reached, and the cellular activities then appear to be "depressed." The maturation stimulating effect of roentgen irradiation is shown in several ways. Young cells stained while living with Janus green and neutral red show more granules stained with the former than with the latter dye. In older cells the neutral red granules predominate. In cells exposed to roentgen rays and stained supravitally with Janus green and neutral red, the granules stained with the latter dye increase in number

5. Isaacs, R., and Danielian, A. C.: Maintenance of Leukocyte Level and Changes During Irradiation: Study of the White Blood Corpuscles Appearing in the Saliva and Their Relation to Those in the Blood, Am. J. M. Sc. **174**:70, 1927.

6. Bunting, C. H., and Huston, J.: Fate of the Lymphocyte, J. Exper. Med. **33**:593, 1921.

7. Taylor, H. D.; Witherbee, W. D., and Murphy, J. B.: Studies on X-Ray Effects: I. Destructive Action on Blood Cells, J. Exper. Med. **29**:53, 1919. Thomas, M. M.; Taylor, H. D., and Witherbee, W. D.: Studies on X-Ray Effects: II. Stimulative Action on the Lymphocytes, J. Exper. Med. **29**:75, 1919.

and those stained with Janus green decrease.[8] This indicates that the cells grow older rapidly when exposed to the effects of radiation.

A second phenomenon which indicates that roentgen irradiation causes the blood cells to mature and to die of senility or to be disposed of as mature cells normally are, instead of being "killed" by the therapy, is observed in a study of the saliva. Normally when a polymorphonuclear leukocyte matures and runs through its life course, it reaches the capillaries of the mucous membranes of the gastro-intestinal tract, especially those of the mouth, and works its way through the lining into the mouth cavity by its own powers of locomotion.[5] The myeloblasts and myelocytes cannot do this; so they accumulate in the blood stream and, under abnormal conditions, as in myelogenous leukemia, enter the peripheral circulation; they are removed only when they mature or die. As soon as a myelocyte matures into a metamyelocyte and young polymorphonuclear leukocyte, it has the power of invading the mucous membrane (diapedesis, leukopedesis). In a normal person about from 5 to 150 leukocytes per cubic millimeter are washed up by the saliva as it bathes the mucous membranes.[5] After roentgen therapy (in patients with cancer or leukemia or in normal animals) the number increases in the saliva, reaching 10,000 per cubic millimeter or more, especially in chronic myelogenous leukemia.[5] This indicates that following the treatment, increased numbers of immature cells are stimulated to become mature enough to wander through the mucous membranes. There are first an increase in the blood count after therapy and then a decrease in the number of cells in the peripheral circulation, and the white cell count approaches nearer normal, with a decrease in the number of immature cells (myelocytes and metamyelocytes).[9] However, the number of myeloblasts may not be reduced, and at times is increased. They have been stimulated not to mature, but to divide and reproduce. This may not be evident in the peripheral circulation, because the presence of a myeloblast in the blood stream is abnormal, but it is well shown in studies of the bone marrow, where the myeloblasts grow. The number of mitotic figures in dividing cells increases in the bone marrow in from twelve to twenty-four hours after irradiation and decreases rapidly after this.[10] The myeloblasts may fill the spaces of the bone marrow and crowd out all other cells. When the bulk of the cells are in this state in the bone marrow, the patient is said to be refractory to roentgen therapy, because

8. Prigosen, R. E.: Vital Staining of Tumor Cells After X-Ray, J. Cancer Research **8**:305, 1924.

9. Minot, G. R., and Spurling, R. G.: Effect on the Blood of Irradiation, Especially Short Wave Length Roentgen-Ray Therapy, Am. J. M. Sc. **168**:215, 1924.

10. Mottram, J. C.: Histological Changes in the Bone-Marrow of Rats Exposed to Radiations from Radium, Arch. Radiol. & Electroth. **25**:197, 1920.

these cells cannot be stimulated to mature and be lost from the body as are the adult cells. The roentgen radiation, however, does not kill them, but stimulates further growth. When small doses are applied over long periods, the number of germinating cells decreases, and aplastic anemia develops. This is always preceded by a period of hyperplasia in which the cells have been stimulated to abnormal growth until the marrow becomes "exhausted."

The stimulation of maturation of the white blood cells is further shown by a study of the age of polymorphonuclear leukocytes in the peripheral circulation. The youngest cells have a single round nucleus; in the older stage, it is a band form, which becomes constricted into two lobes, and then into three, four, five, six or more lobes. When these types of cells are stimulated to grow older, the number of lobes in the nucleus increases. Kennedy and Grover [11] have shown that after roentgen irradiation of normal rabbits the number of cells with one lobe reaches the maximum in three and one-fourth hours; with two lobes in from one to two days; with three lobes, in from four to five days; with four lobes, in from six to seven days and with five lobes and more, after seven days. In other words, within three and one-fourth hours after therapy the number of myelocytes maturing into metamyelocytes begins to increase, and the process continues throughout the rest of the developmental cycle during the following days.

A careful study of the kinds of polymorphonuclear leukocytes during the first fourteen hours after roentgen irradiation shows that the number of one-lobed cells increases rapidly, starting during the first hour, the maximum being reached in three and one-fourth hours, and that the number remains elevated, with only a slight decrease, during the first fourteen hours. In contrast to this, the number of cells with two lobes decreases slowly but definitely, and the number with three, four and more lobes decreases abruptly and markedly during the first hour.[11] The reason for this is evident. The powers of movement of the one-lobed cells through the mucous membranes (leukopedesis) is feeble compared to that of the others,[5] and they do not appear in great numbers in the mouth; those with two lobes can move more rapidly, whereas those with three or more lobes have active powers of locomotion and quickly migrate from the circulation.

There is always a latent period between the time of exposure to the radiation and the therapeutic results. This period represents the length of time that it takes for a cell to mature, to behave as an adult tissue and to suffer its fate. The period varies with the kind of cell and the stage of development at the time of irradiation (the time required for a

11. Kennedy, W. P., and Grover, C. A.: Studies on the Arneth Count: VIII. The Deflection of the Count by X-Rays, Quart. J. Exper. Physiol. **18**:79, 1927.

reticulocyte to become a granular red cell is fifteen minutes; for a myelocyte to become a metamyelocyte, about three and one-fourth hours; for a carcinoma cell in the breast to mature, about two weeks) as well as with the effective dose.

Throughout the changes that take place in the blood cells, no new stages or types appear. There is an orderly progression to either increased cell division or development to maturity. All of the changes after irradiation are steps that appear normally in the life history of the healthy cell, and the changes occur in an orderly manner, exactly as a normal cell grows, but possibly at an accelerated rate. There is no evidence of degeneration of cells before they reach maturity. After this the fate of the cells is similar to that of the normal cells of the same type. Clinically, the blood of a patient with chronic leukemia may be restored to normal either by intensive irradiation with the maximal dose that the skin will permit or by irradiation at frequent intervals with small doses. In the former case, however, the response is more rapid and the normal blood picture is reached days or weeks sooner than when small doses are given. With the small doses there is a greater tendency for the myeloblastic or lymphoblastic tissue to be stimulated to active growth, so that the so-called "refractory" stage of the disease (in reality the stage when most of the cells are blasts) is reached more quickly.

The same process appears to take place in other irradiated tissue, such as cancerous tissue in the breast. However, the mature cells cannot be carried away as can those in the blood stream, so that when they grow old and die in situ there may occur necrosis, changes in the blood vessels, and, possibly, fibrosis. These cells, like those of the blood, have a latent period between the time of irradiation and the clinical response which corresponds to the time necessary for that particular type of cell to mature and to die of senility.

Of the stages in the development of the polymorphonuclear leukocyte, that of the myeloblast or primitive myeloblast is the only one in which the cell can divide and give rise to daughter cells. Cells in stages older than this are on the way to differentiation and never divide. Stimulation during the myeloblastic stage results in increased cell division. This is noted clinically in the exacerbation of symptoms after irradiation in leukemias in the acute (myeloblastic or lymphoblastic) stage. A similar division in growth potentialities is noted in the lymphoblastic and older stages of lymphocytes, erythroblasts and more mature red blood cells. The cells, then, respond by continuing their normal physiologic processes: The myeloblasts, lymphoblasts and erythroblasts divide, and the cells in the older stages continue on the way to maturity. These observations are used clinically in causing immature cells to mature, as in chronic leukemia, or myeloblasts to divide, as in roentgen therapy in

agranulocytosis (granulocytopenia)[12] or induction of remissions in anemia by the same method.[4] Another aspect of the same phenomenon is the resistance to roentgen rays of cells that have a long adult life, such as muscle cells, cells in the fibrous tissue and nerve cells. In cells in this type of tissue maturity is not normally followed by immediate death under physiologic conditions, and maturity stimulated by roentgen rays is not followed by death from senility as quickly as in cells in other tissues, such as leukocytes, germ cells and other cells that normally die shortly after maturity is reached. The muscle, fibrous tissue or nerve cells are, then, not more "resistant" to roentgen irradiation; they merely have a longer adult life and so appear to survive longer after radiation has been applied.

SUMMARY AND CONCLUSIONS

The effect of roentgen irradiation, in both small and large doses, on developing blood cells is stimulating, the result depending on the stage of development of the cells. Cells in the myeloblastic, lymphoblastic or a younger stage are stimulated to rapid reproduction, because such is their growth potentiality at that stage, whereas cells in the myelocytic stage or the medium-sized lymphocytic stage are stimulated to grow through the rest of their life history in an orderly manner, because normally these cells do not divide and multiply. They die or are eliminated as normal, senile cells. There is no evidence of a toxic necrotic action of the roentgen rays when applied in therapeutic doses. The process is hastened by larger doses, so that senility is reached more quickly, giving the impression of a "depressing" action. The period between the application of the roentgen rays and the time when the cells reach senility is the latent period. This corresponds to the time necessary for the cells to mature. The action of roentgen rays on living, blood-forming cells is one of stimulation to divide or to mature in a normal manner and not one of toxic necrosis. Tissue cells which have a long adult life (muscle cells, nerve cells and fibrous tissue cells) appear resistant to roentgen rays, whereas those that have a short adult life (germ cells and leukocytes) die soon after they are "stimulated" to develop to senility. They all have the same susceptibility, but death follows at varying intervals, depending on how long the cells normally survive in their physiologic life.

12. Friedmann, U., and Elkeles, A.: Die Röntgenbehandlung der Agranulozytose, Deutsche med. Wchnschr. **56**:947, 1930. Gager, L. T., and Speer, A. J.: The Roentgen Treatment of Agranulocytosis, Report of Two Cases with Recovery, Am. J. Roentgenol. **27**:40, 1932.

ENDEMIC NUTRITIONAL EDEMA

I. CLINICAL FINDINGS AND DIETARY STUDIES

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The association of edema and starvation, particularly in epidemics, has been recognized for centuries. The commoner causes of the undernutrition are reflected in the terms "famine edema," "war edema," "prison edema," etc., which have been applied to this condition. During the World War edema attracted a great deal of attention, especially in Germany and the Central Powers where the reduction in food supplies made it extremely common. Still more recently it has been studied and reported among the population of certain famine districts in China.[1] The German studies, especially those of Schittenhelm and Schlecht,[2] Jansen,[3] Schittenhelm [4] and Knack and Neumann,[5] are of special interest, since it was shown that this type of edema was associated with a hypoproteinemia, owing presumably to an insufficient supply of protein in the diet. Since then other studies have shown that cases not only of war edema but of other types of nutritional edema (Govaerts,[6] Peters, Bulger and

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1. (*a*) Ling, S. M.: Change of Serum Proteins in Under-Nutrition, Chinese J. Physiol. **5**:1, 1931. (*b*) Weech, A. A., and Ling, S. M.: Nutritional Edema: Observations on the Relation of the Serum Proteins to the Occurrence of Edema and to the Effect of Certain Inorganic Salts, J. Clin. Investigation **10**:869, 1931.

2. Schittenhelm, A., and Schlecht, H.: Über die Ödemkrankheit, Ztschr. f. d. ges. exper. Med. **9**:1, 1919.

3. Jansen, W. H.: Die Ödemkrankheit: Studien über die Physiologie der Unternährung und über die Ödempathogenese, Deutsches Arch. f. klin. Med. **144**: 131 and 330, 1920.

4. Schittenhelm, A.: Ödemkrankheit in Enzyklopaedie der klinische Medizin, Berlin, Julius Springer, 1927, vol. 7, p. 738.

5. Knack, A. V., and Neumann, J.: Beitrag zur Oedemfrage, Deutsche med. Wchnschr. **43**:901, 1917.

6. Govaerts, P.: Recherches cliniques sur le rôle de la pression osmotique des protéines du sang dans la pathogénie des oedemes et de l'hypertension artérielle, Bull. Acad. roy. d. méd. de Belgique **4**:161, 1924.

Eisenman,[7] Peters, Wakeman and Eisenman,[8] and Weech and Ling [1b] are associated with a decrease in the plasma proteins, affecting mainly the albumin fraction. This finding, in the light of Starling's [9] hypothesis, has suggested that the reduction in plasma proteins plays an important rôle in the production of this type of edema.[10] Kohman [11] has produced an edema experimentally in rats by feeding a diet low in protein. Frisch, Mendel and Peters [12] have confirmed Kohman's results and in addition have shown that such protein-poor diets cause a deficiency in the plasma proteins. It has been shown that the edema of nephrosis [13] and of chronic nephritis [14] is closely related to a reduction in plasma proteins, owing, in part at least, to a loss of protein in the urine, and possibly in part to a protein starvation.[14c] The experimental production of edema in dogs by the process of plasmapheresis (Leiter,[15] Barker and Kirk,[16] Shelburne and Egloff [17]) further emphasizes the importance of plasma proteins in relation to edema. So close, in fact, is this relationship that

7. Peters, J. P.; Bulger, H. A., and Eisenman, A. J.: The Plasma Proteins in Relation to Blood Hydration: II. In Diabetes Mellitus, J. Clin. Investigation **1**:451, 1925.

8. Peters, J. P.; Wakeman, A. M., and Eisenman, A. J.: The Plasma Proteins in Relation to Blood Hydration: III. The Plasma Proteins in Malnutrition, J. Clin. Investigation **3**:491, 1927.

9. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**:312, 1895-1896.

10. Weech and Ling.[1b] Schittenhelm and Schlecht.[2] Bruckman, F. S.; D'Esopo, L. M., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration: IV. Malnutrition and the Serum Proteins, J. Clin. Investigation **8**:577, 1930.

11. Kohman, E. A.: The Experimental Production of Edema as Related to Protein Deficiency, Am. J. Physiol. **51**:378, 1920.

12. Frisch, R. A.; Mendel, L. B., and Peters, J. P.: The Production of Edema and Serum Protein Deficiency in White Rats by Low Protein Diet, J. Biol. Chem. **84**:167, 1929.

13. Epstein, A. A.: Further Observations on the Nature and Treatment of Chronic Nephrosis, Am. J. M. Sc. **163**:167, 1922.

14. (*a*) Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, J. Exper. Med. **39**:887, 1924. (*b*) Moore, N. S., and Van Slyke, D. D.: The Relationship Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, J. Clin. Investigation **8**:337, 1930. (*c*) Peters, J. P.; Bruckman, F. S.; Eisenman, A. J.; Held, P. N., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: VI. Serum Proteins in Nephritic Edema, J. Clin. Investigation **10**:941, 1931.

15. Leiter, L.: Experimental Nephritic Edema, Arch. Int. Med. **48**:1 (July) 1931.

16. Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:319 (March) 1930.

17. Shelburne, S. A., and Egloff, W. C.: Experimental Edema, Arch. Int. Med. **48**:51, 1931.

various critical levels of serum albumin, below which edema is almost always present and above which it is usually absent, have been described in different types of edema.[18]

In the last few years a number of cases of nutritional edema with lowered serum protein have been reported in this country.[19] These have been sporadic cases, in most of which the edema accompanied some disease, such as tuberculosis, diabetes, cancer or gastro-intestinal disorders, which was responsible for an insufficient intake or an inadequate absorption or utilization of food. In infants a similar sporadic edema occurs as a result of improper diet, or in association with various diseases.[20] The existence of uncomplicated epidemic or endemic nutritional edema has scarcely been suspected.

During the spring and summer of 1929, our attention was first attracted to a number of patients with an obscure edema. They complained of swelling, usually of the feet and legs but sometimes of the face and hands as well. Many of them gave a history of previous attacks. Besides the edema, many complained of pain and tenderness in the legs and of indefinite pains in the joints. Although a few had incidental conditions not related to the edema, the swelling was the only complaint in the great majority. Most of the patients were women. Examination showed a soft pitting edema, but investigation failed to reveal any of the usual causes. It was first thought that the edema was due to a mild heart failure, but the cardiovascular findings were insufficient to explain it. The urine and renal functional tests were normal. Most of the patients were somewhat anemic, but with the possible exception of one case the anemia was not severe enough to cause the edema, and some of the patients had no anemia. The idea that these might be cases of nutritional edema suggested itself, though there was no obvious cause for a widespread undernutrition and the economic situation at that time was generally satisfactory. It was known, however, that the customary diet of a large part of the population of this part of Tennessee was of a character which might result in a low protein intake, consisting as it did in the main of highly milled cereals, fats, cooked leafy vegetables and relatively little animal protein. Therefore the total serum protein was determined in several instances. It was found to be normal or higher than normal. Before arrangements for a more complete study could me made, it was late summer, no new cases appeared and

18. Weech and Ling.[1b] Moore and Van Slyke.[14b] Peters et al.[14c]

19. Peters, Bulger and Eisenman.[7] Peters, Wakeman and Eisenman.[5] Landis, E. M., and Leopold, S. S.: Inanition Edema Associated with Tuberculous Enteritis, J. A. M. A. **94**:1378, 1930. Wolferth, C. C.: Inanition Edema Associated with Alimentary Disturbance in Adults, M. Clin. North America **8**:785, 1924.

20. Unpublished observations, Department of Pediatrics, Vanderbilt University Hospital.

the old patients lost their edema. However, similar cases have appeared each year since, until a total of more than fifty have been observed. They are most often first seen in the late winter and spring, and increase in number through the spring and early summer. Toward fall new cases fail to appear, and the old patients lose their edema. It is the purpose of this paper to present the clinical findings in thirty-one of these patients who were studied fairly completely, together with a study of the diet of twelve of them. The results of a study of the serum proteins and of the nitrogen balance are reported in the succeeding paper.

MATERIAL AND METHODS

With two exceptions, all the patients were studied and followed in the outpatient department. In addition to the usual history and physical examination, the study included, in most of the cases, repeated urinalysis, the usual estimation of erythrocytes, leukocytes and hemoglobin and study of a stained smear, the Wassermann and phenolsulphonphthalein renal functional tests, an orthodiagram of the chest, an electrocardiogram, determination of the nonprotein nitrogen of the blood and a determination of the basal metabolic rate. A gastric analysis, examination of the stool and a reticulocyte count were made in a number of instances. In a few of the earlier cases the presence of edema was checked by the salt solution absorption test (McClure and Aldrich[21]). The serum proteins were determined at the time of the first visit or within a few days thereafter. The various laboratory examinations were made according to the usual standard methods. Nonprotein nitrogen was determined according to the method of Folin.[22] The basal metabolic rate was determined with a Roth-Benedict apparatus. In a number of the later cases the hemoglobin was determined with a calibrated Sahli instrument and the values expressed in grams of hemoglobin per hundred cubic centimeters, but for convenience all values are expressed in Sahli units. In those cases in which an achlorhydria was found with a simple test meal the examination was repeated after the injection of histamine.

The diet of twelve of the patients was ascertained before the institution of treatment or experimental procedures by having the patient keep an accurate record of the food eaten for a number of days. Printed slips were provided on which the amounts and kind of food taken each day were recorded. The procedure was carefully explained to the patient, not only by the physician but also by a social worker who sometimes visited the patient at home during this period to assist in keeping the record and to check its accuracy. From this record the total calories, and the total protein, animal protein, fat and carbohydrates were calculated.[23]

RESULTS

The principal clinical data are summarized in table 1 and may be presented briefly as follows: The ages of the patients varied from 20

21. McClure, W. B., and Aldrich, C. A.: Time Required for the Disappearance of Intradermally Injected Salt Solution: Preliminary Report of Observations, with Special Reference to Cases of Edema, J. A. M. A. **81**:293, 1923.

22. Folin, O.: Laboratory Manual of Biological Chemistry with Supplement, ed. 4, New York, D. Appleton and Company, 1925.

23. Mrs. Stow and Miss Winckler, Directors of Dietetics of the Vanderbilt University Hospital, performed these calculations.

to 76, the majority being between 30 and 60. Eighteen were colored and thirteen were white. There were twenty-six women and five men. The duration of the edema varied from two days to a period of several years. It had been present a week or less in seven, from one to four weeks in seven, for several months in eight and for a year or more in five. In the latter the disease had been present intermittently. The duration was unknown in four cases. Edema of either the feet or the legs alone, or of the two together, occurred in twenty-one. In nine there was swelling of the face, hands or both, in addition to the swelling of the feet and legs. In one case the face alone was swollen. Fourteen patients gave a history of previous similar attacks and in two there was a history of swelling of the face and hands which was not present at the time they were observed. The amount of edema has been recorded as follows: slight but definite pitting edema of the feet and lower one third of the leg, +; moderate pitting edema of the same regions, ++; pitting edema of the feet and lower two thirds of the leg, +++, and pitting edema up to the knees, ++++. The quantitative measure of edema is of course unsatisfactory, owing in part to the well known difficulties in estimating the degree of edema and in part to diurnal and other variations in the edema which will be discussed. The degree of edema was + in sixteen, ++ in six, +++ in five and ++++ in two. The edema was questionable or absent at the time of examination in two. In several cases the edema was greater than the maximum indicated by this system of grading.

The heart was entirely normal in twenty-seven. As might be expected from the ages of some of the patients, a few showed some cardiac abnormalities, but in no case was there evidence of congestive failure other than edema. Three had a slight or questionable enlargement of the heart and only one showed as much as a moderate enlargement. The latter had occasional extrasystoles, and one (case 18) had a bundle branch block shown by electrocardiogram. The blood pressure was normal in nearly all, the systolic pressure being below 150 in all but two, with corresponding diastolic pressures. In case 18, with slight cardiac enlargement, the pressure was 180 systolic and 98 diastolic; in case 19, with moderate enlargement, 200 systolic, 110 diastolic. In one case the blood pressure was not determined.

A slight albuminuria was present in four, in one on a single occasion only. Casts were found only three times and an occasional red blood cell was found in uncatheterized specimens (women) twice. The phenolsulphonphthalein excretion was above 50 per cent in the twenty-three in whom the test was done, and above 60 per cent in nineteen. The nonprotein nitrogen of the blood was within normal limits in every case.

TABLE I.—*Summary of Clinical Data in Thirty-One Patients with Edema*

Case, Sex, Patient	Date	Age	Height, Cm.	Weight, Kg.	Edema: Amount	Edema: Duration	Edema: Location	Edema: Previous Attacks	Heart	Blood Pressure, Mm. Hg	Kidney: Albumin and Casts	Kidney: Cells	Kidney: Phenolsulphonphthalein, per Cent	Blood: Hemoglobin, per Cent	Blood: Red Cells, Millions	Blood: Nonprotein nitrogen, Mg. per 100 Cc.	Blood: Wassermann Test	Free Hydrochloric Acid	Basal Metabolic Rate, per Cent	Salt Solution Absorption Time, Min.
1, ♀ M. T.	6/18/29	35	170.2	73.1	+++	3 weeks	Feet, legs, hands	+	Normal	110/ 64	Albumin, 0 Casts, 0	0	75	52	3.90	24.0	Positive	0	— 8	4
2, ♀ M. N.	7/19/29	24	165.1	55.4	+	Intermittently	Legs	+	Normal	100/ 60	Albumin, 0 Casts, 0	Few white	75	68	3.24	24.0	Doubtful	+	+ 2	40
3, ♀ W. B.	7/10/29	32	167.6	88.6	++	?	Feet, legs	+	Slightly enlarged (x-ray)	120/ 74	Albumin, 0 Casts, 0	Few white	65	40	3.23	23.0	Negative	+	—10	13-19
4, ♀ C. D.	7/23/29	37	160.0	50.9	+	3 years, intermittently	Feet, legs	+	Normal	120/ 70	Albumin, 0 Casts, 0	Occas.	75	35	3.42	32.4	Positive	+	+ 3	60
5, ♀ Q. S.	3/25/30	24	161.3	70.9	+	1-2 months	Hands, legs	0	Normal	114/ 64	Albumin, 0 Casts, 0	4-5 white	80	74	3.95	25.0	Negative	+	—10	13-19
6, ♀ A. P.	4/12/30	33	172.7	51.1	++	Intermittently	Feet, legs	+	Slightly enlarged	140/100	Albumin, 0 Casts, 0	5 white	92	60	4.15	20.0	Negative	..	+ 2	..
7, ♀ L. A.	4/30/30	42	163.8	76.8	+	3 weeks	Feet, legs	0	Normal	118/ 80	Albumin, 0 Casts, 0	Many white	65	70	4.26	27.2	Negative	+ Hypo.	+ 3	45
8, ♂ J. L.	7/15/30	45	167.6	52.4	+	3 days	Feet, legs	0	Normal	120/ 80	Albumin, 0 Casts, 0	0	..	62	3.81	25.6	Negative	..	....	..
9, ♀ M. H.	7/ 9/30	34	152.4	80.4	+++	4-5 days	Feet, legs	+	Normal	120/ 80	Albumin, 0 Casts, 0	0	50	60	5.30	26.8	Negative	+	+12	..
10, ♀ E. A.	7/25/30	45	163.8	72.7	+	6 months	Feet, legs	0	Normal left ventricular preponderance	112/ 60	Albumin, 0 Casts, 0	Red, white	..	..	....	30.7	Negative	..	....	..
11, ♀ A. D.	7/30/30	50	.....	....	+	Several months	Feet, legs	+	Normal	112/ 70	Albumin, 0 Casts, 0	Few white	70	85	4.24	30.7	.....	..	+15	..
12, ♀ W. J.	9/30/30	37	157.5	45.9	+	2½ months	Feet, legs	0	Normal	130/ 94	Albumin, 0 Casts, 0	0	65	80	4.06	27.2	Negative	..	— 4	..
13, ♀ V. H.	11/19/30	50	165.1	50.9	+	Intermittently (years)	Feet, legs	0	Normal	125/ 80	Albumin, 0 Casts, 0	Few white	60	68	3.71	31.5	Negative	..	— 7	Legs, 15 Arms, 20
14, ♀ M. B.	12/ 9/30	55	162.9	49.8	?	?	Feet	+	Normal	130/ 80	Albumin, 0 Casts, 0	0	..	..	....	25.0	Negative	..	—10	..
15, ♀ J. S.	3/ 4/31	55	157.5	44.0	++	?	Feet, legs	?	Normal	160/ 70	Albumin, trace Casts, 0	Occas. white	..	64	4.01	31.5	Negative	+	....	..

16, ♀ G. R.	3/ 9/31	30	166.4	81.5	+++	3 months	Feet, legs	0	Normal	136/ 94	Albumin, trace Casts, 0	Occas. white	70	78	4.29	26.6	Positive	+	+12	..
17, ♀ K. V.	3/18/31	48	160.7	46.3	++++	1 week	Feet, legs, face	0	Normal	135/ 80	Albumin, + later, 0 Casts, occas. cellular and granular	Occas. white	80	52	4.62	35.2	Negative	+	— 7	..
18, ♂ A. C.	3/20/31	62	170.2	62.6	+	10 days	Ankles	0	Bundle branch block; slight enlargement to left	180/ 98	Albumin, 0 Casts, few (hyaline)	Many white	50	65	4.28	31.5	Negative	..	....	..
19, ♂ S. M.	4/ 6/31	76	172.7	61.3	++++	4 weeks	Feet, legs	+	Moderate enlargement; occasional extrasystole	200/110	Albumin, 0 Casts, 0	0	65	80	4.95	24.4	Positive	..	....	..
20, ♂ J. N.*	4/23/31	60	172.7	65.4	++	1 week	Feet, legs	+	Normal	106/ 60	Albumin, 0 Casts, occas. hyaline and granular	Few white	55	83	3.79	30.7	Negative	+ (1928)	....	..
21, ♀ S. G.	4/13/31	50	154.9	54.5	+	Intermittently over a year	Eyes, feet, legs	+	Normal	124/ 70	Albumin, 0 Casts, 0	0	75	..	....	31.5	Negative	..	+24	..
22, ♂ J. R.	4/28/31	20	184.2	84.7	+++	3 days	Face, hands, feet, legs	0	Normal	118/ 76	Albumin, 0 Casts, 0	Occas. white	70	59	3.91	27.0	Negative	+	....	..
23, ♀ J. W.	5/27/31	52	136.2	59.0	0	2 weeks	Feet, legs, hands (?)	0	Normal	140/ 90	Albumin, 0 Casts, 0	10-15 white	..	..	....	25.0	Negative	..	....	..
24, ♀ E. H.	6/ 6/31	27	168.3	50.9	+	?	Legs	0	Normal	100/ 60	Albumin, 0 Casts, 0	Occas. white	55	56	3.98	25.0	Negative	..	....	..
25, ♀ A. W.	6/23/31	40	180.3	90.9	+	3 months	Face, legs	+ including hands	Normal	140/ 88	Albumin, 0 Casts, 0	0	90	76	4.53	29.5	Negative	+	....	..
26, ♀ L. R.	6/23/31	41	162.7	....	+	1 week	Feet, legs	+ also face, hands	Normal	.....	Albumin, 0 Casts, 0	0	..	85	4.65	26.0	Negative	..	+ 9	..
27, ♀ M. R.	7/ 7/31	40	162.6	73.6	±	4-5 months	Legs	0	Normal	116/ 82	Albumin, 0 Casts, 0	6-8 white	70	69	3.86	26.0	Negative	+	— 9	..
28, ♀ K. S.	7/ 8/31	29	154.9	50.6	+	1 week	Feet, legs, face	+	Normal	126/ 78	Albumin, 0 Casts, 0	0	..	63	3.78	35.0	Negative	..	....	..
29, ♀ B. V.	7/ 3/31	32	160.0	88.6	+	Several weeks	Feet, legs	0	Normal	110/ 68	Albumin, 0 Casts, 0	2-4 white	82	71	3.90	22.6	Negative	+	....	..
30, ♀ M. R.	7/27/31	52	170.2	67.5	+++	3 weeks	Feet, legs, face	0	Normal	148/100	Albumin, 0 Casts, 0	0	..	..	....	32.4	Negative	..	....	..
31, ♀ L. D.	7/29/31	40	154.9	39.8	+	6 weeks	Face	0	Normal	104/ 62	Albumin, 0 Casts, 0	0	60	83	4.70	26.6	Negative	..	....	..

* Treated previously for pellagra. ♂ indicates male; ♀, female.

A secondary anemia of slight or moderate severity was found in nearly all the patients. The red cells were above 3,000,000 in all that were examined. The hemoglobin ranged from 40 to 85 per cent (Sahli). The color index was over 1 in but a single case. In the few cases in which counts were made, the reticulocytes were found to be very few.

The Wassermann reaction was positive in four, doubtful in one and not obtained in one. In none was there clinical evidence of active syphilis.

A gastric analysis was done in fifteen cases. Free hydrochloric acid was present in normal amounts in twelve, and hypo-acidity in one; in two there was achlorhydria even after an injection of histamine. The stools were examined in twelve cases. One showed mucus, meat fibers and flagellates. In one case Trichuris, Endolimax nana and a positive guaiac reaction were found on one occasion only; subsequent examinations gave negative results.

The basal metabolic rate was determined in seventeen of the patients. Values within the normal range (+ or — 10) were found in all but four. The rate was + 12 in two, and + 15 and + 24 in one each. Single determinations were made in these four. Only one patient presented signs suggesting thyrotoxicosis.

In a few of the earlier cases the salt solution absorption test for edema was made. The absorption time varied from four to sixty minutes. In all but one the time was less than forty-five minutes.

Severe undernutrition was uncommon, and practically no one was emaciated even after the loss of edema. Only sixteen were under their calculated ideal weight, while several of the thirteen who were overweight were actually obese. The weight was not recorded in two. No allowance has been made for the edema in these calculations, and it is probable that a number of these who were apparently slightly overweight were actually underweight. However, even those who were definitely overweight often gave a history of loss of weight preceding the appearance of the edema, and such losses were observed in patients as they were followed during periods of edema and of freedom from edema.

The average daily intake of protein, animal protein, carbohydrate and fat and the total calories in twelve cases are summarized in table 2. The calculated basal caloric requirement in each case is presented for comparison. Because of the relatively short periods, single days in which an exceptionally low intake was recorded have been omitted from these calculations in two cases (cases 7 and 29). In every instance but one the caloric value of the diet is seen to be below the calculated basal requirements. Since all were outpatients and more or less active, the deficiency is more striking. However, though it is believed that the

records are fairly accurate, the total caloric intake was probably somewhat greater than is recorded. Considerable amounts of fat were used in cooking and have not been included in these calculations. The daily records showed considerable variation, and had the study been made over a longer period, it seems probable that a higher average would have been found. Nevertheless, the total caloric intake was undoubtedly very near the bare maintenance level in most instances. The average daily intake of protein was low, ranging from 20 to 52 Gm. daily. In eight cases the protein intake was below the usually accepted minimum of from 0.5 to 0.7 Gm. per kilogram,[24] and in the rest was below 1.0 Gm. per kilogram. Animal protein amounted to from 41 to 70 per cent of the total protein. The rather high ratio of animal to total protein was at first surprising, but on reflection it was apparent that this finding

TABLE 2.—*Average Daily Food Intake Before the Institution of Treatment*

Case	Weight	Calculated Basal Requirement, Calories	Intake							Number of Days
			Total Calories	Total Protein, Gm.	Protein per Kg., Gm.	Animal Protein		Fat, Gm.	Carbohydrate, Gm.	
						Gm.	Per Cent			
5	69.8	1,554	790	31	0.44	18	58	...	...	6
7	76.8	1,590	390	26	0.33	15	57	58	101	6
9	80.4	1,551	907	31	0.38	15	48	41	111	6
13	50.9	1,294	1,106	45	0.88	31	69	46	127	6
16	81.5	1,664	1,396	41	0.41	18	44	76	137	6
17	46.3	1,253	887	31	0.66	17	55	31	121	4
18	63.6	1,524	1,012	38	0.59	23	61	59	104	4
19	61.3	1,517	515	20	0.32	12	60	26	48	5
21	54.5	1,302	1,377	52	0.95	34	65	79	114	5
27	73.6	1,555	1,018	33	[a]0.44	18	55	33	148	5
28	50.6	1,305	854	22	0.43	9	41	34	112	6
29	88.6	1,638	1,140	44	0.49	31	70	38	123	6

might have been expected, since the usual diet contained so little total protein that any animal protein present must have made up the greater part of it.

COMMENT

These cases of edema differ in several respects from cases of nutritional edema previously reported, particularly those seen in epidemics. Clinically there is presented a mild edema, endemic in nature, with apparently a fairly high incidence among the part of the population from which these patients are drawn, and with a pronounced tendency to a seasonal (spring and summer) incidence. The edema was rarely as great as that reported among the starving populations during the war or more recently from famine districts in China.[1] Neither were the patients greatly undernourished. This absence of severe undernutrition also serves in part to distinguish these cases from those in which edema occurs in association with some disease which causes a severe under-

24. Sherman, H. C.: Protein Requirement of Maintenance in Man and the Nutrient Efficiency of Bread Protein, J. Biol. Chem. **41**:97, 1920.

nutrition. It should be emphasized that in the cases reported here such diseases were absent, and, except for occasional and incidental conditions not related to the edema, the latter was the principle complaint. It is this feature which particularly distinguishes them from the usual case of sporadic nutritional edema.

In comparing further these cases with those observed during the War, or more recently in China, there is noted a general absence of the bradycardia, hypotension, subnormal body temperatures and lowered metabolic rate frequently present in the latter. The tendency to tachycardia and shortness of breath on exertion, observed in cases of war edema, was noted occasionally. Unusual fatigue and loss of strength were infrequent. In both groups the heart and kidneys were essentially normal. In the present study no information was obtained regarding polyuria, which was a rather prominent feature in cases of war edema. A secondary anemia was apparently more frequent in our series, and there were no cleancut cases of blood concentration with a high red cell count and hemoglobin content, such as were observed by Schittenhelm and Schlecht [2] and by Jansen.[3] All these observations are consistent with the mild nature of the disease and the absence of severe general undernutrition.

The mild nature of the disease is explained by the absence of a severe and relatively acute deprivation of food. In spite of the apparently great reduction in food intake, as shown in table 2, there is reason to believe that the dietary deficiency is principally a protein shortage, with the total caloric intake near the minimal requirements. On the other hand, this dietary deficiency had probably existed for years. The dietary studies were made at the time of the appearance of edema, when there might well have been a temporary reduction in food intake sufficient to produce symptoms in a person whose diet was ordinarily barely sufficient. The periods are too short to permit the assumption that the caloric intake represented the average over a long period of time. Furthermore, the diet is more a matter of custom and habit than of necessity. This conception of the nature of the dietary insufficiency is supported by the fact that few of the patients were greatly underweight and at least half were of normal weight or above, though even the latter often gave a history of loss of weight some time before the onset of the edema. To some extent at least, the absence of a greater edema may be due to the relatively low water content of the diet as compared with the diet in the cases of war edema.

The insufficiency of protein is clearly shown by these studies even though allowance is made for the fact that the amounts may have been somewhat greater at some periods. In general, the values are less than those given by Jansen [3] in his cases of war edema (group A), and in

most instances are well below the usual minimum requirements. They are more significant in view of the low caloric intake, since it is known that though nitrogen equilibrium may be maintained in a protein intake as low as recorded here, it is necessary that the total calories be high. In addition, no allowance has been made for the loss of nitrogen in the stool, which may have been greater than usual on a diet of this type, or for the availability of some of the types of protein in the diet. On the other hand, interference with absorption due to diarrhea or other disease of the gastro-intestinal tract was apparently not a factor. Further evidence of protein starvation is obtained from the studies of nitrogen balance reported in the succeeding paper.

The possibility that the edema in these cases is present as a part of some specific deficiency disease (avitaminosis) must be considered. The same question was raised in connection with the cases during the War and particularly in connection with similar cases of edema disease seen in India.[25] A mild or abortive form of beriberi seems to be the only recognized disease compatible with the findings which these patients present. Aside from the edema, the only feature which suggests beriberi is the occurrence of mild pain in the extremities and tenderness over the affected areas. This tenderness occurs in other forms of edema, however, and while it is impossible to prove that these are not mild cases of beriberi, the absence of more definite peripheral nerve changes, the presence of normal reflexes and the lack of fully developed and characteristic cases among so many mild ones makes beriberi unlikely.

The greater frequency at certain seasons is difficult to explain. A preliminary inquiry into the dietary habits of the patients did not reveal any particular difference between the summer and winter months. It might be that during the colder weather the greater caloric requirements lead to a relatively greater food deficiency, which finds expression in the occurrence of edema some time later. Nutritional edema is particularly affected by variations in the fluid intake, and it is possible that the greater incidence in warmer weather is related to a larger intake of water at that time. An increase in venous pressure during warm weather may favor the formation of edema, but it is difficult to reconcile this with the tendency for the edema to disappear in the late summer.

The amount of edema varied considerably from time to time, a finding which has been observed by others. These changes occurred with considerable rapidity, and a well marked edema might disappear almost entirely in a day or so, only to reappear again. These changes occurred not only in association with such well known factors as rest and activity (diurnal and nocturnal variations), but in the absence of any known

25. Ray, C.: Epidemic Dropsy: Its Blood Picture, General and Biochemical, Indian J. M. Research **15**:67, 1927.

cause and often without any relation to treatment. Similar changes in the edema without change in the serum protein were observed by Moore and Van Slyke [14b] in cases of chronic nephritis and by Shelburne and Egloff [17] in dogs made edematous by plasmapheresis.

SUMMARY

The clinical findings in a group of patients whose principal complaint was a mild edema, apparently nutritional in nature, are reported. The diet of twelve of these patients was determined before the institution of treatment or experimental studies. In all but one the total calories were below the basal requirements. The average protein intake ranged from 20 to 52 Gm. daily, and was below the usual minimum (from 0.5 to 0.7 Gm. per kilogram) in all but four cases. It is believed that these patients were suffering from a chronic dietary deficiency, particularly a shortage of protein, with an accompanying nutritional edema.

DIFFUSIBLE CALCIUM OF THE BLOOD STREAM

V. INFLUENCE OF AGENTS WHICH AFFECT BLOOD CALCIUM ON CALCIUM DISTRIBUTION AND INORGANIC PHOSPHATE OF THE SERUM

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The use of agents capable of influencing the calcium content of the blood in the treatment of many pathologic conditions has become a widespread medical procedure.[1] When there is any rational basis at all, the purpose of these reagents is to counteract a deficiency, presumed or real, in blood or tissue calcium. In some instances, it is true, the treatment is given, not for the direct effect on calcium, but for secondary effects such as to decrease hemorrhagic tendencies or to relieve edema. A sound rational basis for calcium therapy depends on an extensive knowledge of the influence of the agents commonly employed on the biochemistry of the body calcium and other bodily constituents that are interrelated with the calcium. Since it is naturally difficult to study the whole of the body calcium, attention has been given mainly to the effect on the blood calcium. Many studies have been devoted in years past to agents capable of influencing the level of blood calcium. In the main, these agents consist of calcium-containing compounds, extracts of the parathyroid gland, irradiation with ultraviolet light and various preparations of the antirachitic vitamin D. The bulk of these studies has been confined to the measurement of the changes produced in the total serum calcium alone.

Eli Lilly & Co. furnished the parathyroid extract-Collip used in the experiments.

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1. (*a*) Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, chap. 16. (*b*) Herzfeld, E.; Lubowski, H., and Kruger, R.: Die klinische Bedeutung des Serumkalkspiegels beim Menschen; Kritische Uebersicht (1923-1928), Folia haemat. **41**:73 (May) 1930. (*c*) Cantarow, A.: Calcium Metabolism and Calcium Therapy, Philadelphia, P. Blakiston's Son & Co., 1931.

As a result of the many studies on the biochemistry of blood calcium, it is generally accepted that the calcium is present only in the plasma, and in the plasma it exists in at least two distinct fractions, commonly termed diffusible and nondiffusible calcium. These two fractions are distinguishable by the ability of the diffusible calcium to pass through a colloid impermeable membrane while the nondiffusible calcium is held back by such a membrane. It is now also widely held that the diffusible calcium is physiologically active while the nondiffusible calcium is apparently physiologically inert. Also, to add to the complexity, it has been suggested that there exists a functional relationship between the calcium, the proteins and the inorganic phosphate of the blood serum.[2] It is readily seen, then, that the study of the changes in the total calcium is not sufficient for a complete description of the action of substances influencing the level of the blood calcium. Since, as far as we were aware, no complete determination of the effect of agents capable of influencing the blood calcium had been carried out on the diffusible calcium, nondiffusible calcium and inorganic phosphate concurrently, such a series of experiments was undertaken by us. Sweet milk, acidified milk, a number of calcium salts and parathyroid extract were used as test substances in the experiments.

The purpose of these studies was not only to accumulate data which would be serviceable in securing a fundamental basis for calcium therapy, but also to obtain by these experiments a deeper insight into the postulated relationships between diffusible calcium, nondiffusible calcium proteins and inorganic phosphate.

When a closer consideration is given to the factors underlying the connection between these quantities, it becomes probable, in the light of present-day knowledge, that in the first instance the relationship of the phosphate level is with the diffusible calcium, while that of the protein is with the nondiffusible fraction. Any connection between inorganic serum phosphate and calcium would be logically expected to spring from the rôle of these two ions in the mechanism of calcification, a subject which has been extensively studied in vitro by Shipley, Kramer and

2. (*a*) Loeb, R. F., and Nichols, E. G.: Factors Influencing the Diffusibility of Calcium in Human Blood Serum, J. Biol. Chem. **72**:687 (April) 1927. (*b*) Greenberg, D. M., and Gunther, L.: On Determination of Diffusible and Non-Diffusible Serum Calcium, ibid. **85**:491 (Jan.) 1930. (*c*) Salvesen, H. A., and Linder, G. C.: Inorganic Bases and Phosphates in Relation to Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, ibid. **58**:617 and 635 (Dec.) 1923. (*d*) Howland, J., and Kramer, B.: Factors Concerned in the Calcification of Bone, Tr. Am. Pediat. Soc. **34**:204, 1922. (*e*) Peters, J. P., and Eiserson, L.: Influence of Protein and Inorganic Phosphorus on Serum Calcium, J. Biol. Chem. **84**:155 (Oct.) 1929.

Howland,[3] Robison,[4] Holt, La Mer and Chown,[5] Sendroy and Hastings,[6] Shear and Kramer[7] and many others. The basic idea of all these studies is that calcification is dependent on the solubility product of some sparingly soluble calcium and phosphate containing salt. If the solubility product of such a salt also governs the level of the calcium and phosphate ion in the blood stream, it is readily seen that the calcium content should vary inversely as the inorganic phosphate of the serum. Since it is the calcium ion which is involved in this relationship, and since in the blood it is the diffusible fraction which contains the calcium ion, it follows that the relationship which exists between the blood phosphate and calcium is primarily concerned with the diffusible calcium.

It should be noted that the inverse relationship postulated between calcium and inorganic phosphate is not always borne out, as is shown by the analytic results of Stearns and Knowlton[8] on the blood of children.

Reasoning in a similar way, since it is held that the nondiffusible calcium is combined in a nonionic way with the serum proteins,[9] the level of the proteins primarily affects the nondiffusible calcium. However, it has been pointed out by us[2b] that the diffusible calcium and nondiffusible calcium are not independent of each other, according to the results of experiments in vitro. Instead, when the protein and p_H are kept constant, the level of the nondiffusible calcium varies directly with the content of diffusible calcium. In this way, all four quantities have an influence on each other. By the use of agents influencing blood calcium and thus obtaining values far out of the ordinary range, the relationships that obtain between diffusible calcium, nondiffusible calcium, inorganic phosphate and protein would be expected to be accentuated and thus made more readily interpretable. Furthermore, su h

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3. Shipley, P. G.; Kramer, B., and Howland, J.: Calcification in Vitro, Biochem. J. **20**:379, 1926.

4. Robison, R.: Possible Significance of Hexosephosphoric Esters in Ossification, Biochem. J. **17**:286, 1923.

5. Holt, L. E.; La Mer, V. K., and Chown, H. B.: Studies in Calcification: Solubility Product of Secondary and Tertiary Calcium Phosphate Under Various Conditions, J. Biol. Chem. **64**:509 and 576 (July) 1925.

6. Sendroy, J., and Hastings, A. B.: Studies on Solubility of Calcium Salts, J. Biol. Chem. **71**:783 and 797 (Feb.) 1927.

7. Shear, M. J., and Kramer, B.: Composition of Bone: Equilibration of Serum with Dicalcium Phosphate, J. Biol. Chem. **86**:677 (April) 1930.

8. Stearns, G., and Knowlton, G. C.: Lack of Relationship Between Calcium, Protein, and Inorganic Phosphorus of Serum of Non-Nephritic Children, J. Biol. Chem. **92**:639 (Aug.) 1931.

9. Loeb.[2a] Greenberg, D. M.: Electrical Transference of Calcium in Blood Serum Protein Solutions, J. Biol. Chem. **79**:177 (Sept.) 1928. Shear, M. J., and Offner, M. M.: Composition of Bone: Binding of Calcium Ions by Serum, ibid. **91**:291 (April) 1931.

experiments have the value that they are performed in vivo, in the organism itself, and thus have a greater significance for the biochemistry of blood calcium than experiments in vitro.

At this point it is well to consider some objections that have been raised against the methods employed in determining diffusible calcium. From time to time such objections have been raised in the literature. For the present, we shall confine ourselves to some recent statements on the subject, noting that these objections are not wholly new. Osnato, Killian, Garcia and Mattice,[10] in summarizing the work done by means of ultrafiltration and compensation dialysis, pointed out that a wide variation in values has been obtained, ranging from 39 to 75 per cent of the total calcium. On the same subject, Morgulis and Perley[11] stated: "The situation is not much more encouraging when we consider the diffusible and non-diffusible fractions of the serum or plasma calcium, because the results of different investigators are so much at variance and the methods of fractionating the calcium, namely compensation dialysis and ultrafiltration are not above criticism from a theoretical point of view." Hunter[12] again brought up the criticism that the results of ultrafiltration may be affected by the time of filtration and the pressure employed.

In a recent publication, one of us (Dr. Greenberg[13]) has experimentally shown that ultrafiltration of electrolytes partakes of the nature of a Donnan membrane distribution, which leads to the corollary that ultrafiltration and compensation dialysis are analogous in principle. Even so, it is our opinion that the ultrafiltration method is superior to compensation dialysis in the determination of diffusible calcium, since no artificial dialysis liquid employed is completely balanced against all the constituents of the serum. This defect plays no part in ultrafiltration. The time of filtration and the pressure employed actually are of minor importance, as has already been pointed out in a previous communication.[2b] The all-important requirement for obtaining correct results by ultrafiltration is the use of proper membranes, and the preparation and testing of such membranes have also been considered in the communication just mentioned.

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10. Osnato, M.; Killian, J. A.; Garcia, T., and Mattice, M. R.: Comparative Chemical Studies of Blood and Spinal Fluid in Epilepsy, Brain **50**:581 (Oct.) 1927.

11. Morgulis, S., and Perley, A. M.: Studies on Cerebrospinal Fluid and Serum Calcium, with Special Reference to Parathyroid Hormone, J. Biol. Chem. **88**:169 (Aug.) 1930.

12. Hunter, D.: Critical Review: Metabolism of Calcium and Phosphorus and Parathyroids in Health and Disease, Quart. J. Med. **24**:393 (April) 1931.

13. Greenberg, D. M., and Greenberg, M.: Ultrafiltration: I. Ultrafiltration of Electrolytes from Alkali Caseinate Solutions, J. Biol. Chem. **94**:373 (Dec.) 1931.

In some instances, it is true, extremely astonishing and doubtful results have been published. As an illustration, we shall consider one such instance on which we had the opportunity to check. Emerson [14] reported extremely low values for the diffusible calcium of jaundiced dogs, values in some instances of less than 2 mg. per hundred cubic centimeters of serum. He also reported a continuous increase and terminally high values for both the total and the diffusible calcium in dogs in which a bile fistula was produced by a cholecystonephrostomy. The published figures for the diffusible calcium in jaundice by us [15] and by Snell and Greene [16] throw grave doubt on Emerson's figures. Drs. Werner Schmidt and C. L. A. Schmidt permitted us to make a series of analyses on a dog in which a bile renal fistula had been produced. The

TABLE 1.—*Calcium Distribution in a Dog in Which a Bile-Renal Fistula Was Produced*

Date	Diet	Total Calcium	Diffusible Calcium	Plasma Carbon Dioxide, % by Vol.
Feb. 15, 1929	Bile added	9.70	5.70	55.6
Feb. 18, 1929	Bile added	9.60	5.60	58.3
Feb. 26, 1929	Bile free since Feb. 18, 1929	9.30	5.50	61.9
March 6, 1929	Bile free since Feb. 18, 1929	10.20	5.10	55.3
March 11, 1929	Bile free since Feb. 18, 1929	10.4	5.70	40.5
April 12, 1929	Cod liver oil added since March 11, 1929	10.1	5.80	43.2

results obtained are given in table 1, and, again contrary to Emerson's figures, show very little change on a bile-free diet during a period of forty-five days. We point this out to illustrate that the indiscriminate use of all the published data in criticism of a method is not justifiable.

The best answer to the criticisms and the best justification for the validity of the diffusible calcium determination are that a host of workers in widely separated laboratories have obtained consistent and concordant results by the methods that we have employed.[17]

14. Emerson, W. C.: Distribution of Calcium in Jaundiced and Acholic Dogs, J. Lab. & Clin. Med. **14**:122 (Nov.) 1928.

15. Gunther, L., and Greenberg, D. M.: Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930.

16. Snell, A. M., and Greene, C. H.: Calcium in Serum in Jaundice, Am. J. Physiol. **92**:630 (April) 1930.

17. Pincus, J. B.; Peterson, H. A., and Kramer, B.: Study by Means of Ultrafiltration of Condition of Several Inorganic Constituents of Blood Serum in Disease, J. Biol. Chem. **68**:601 (June) 1926. Liu, S. H.: Comparative Study of Effects of Various Treatments on Calcium and Phosphorus Metabolism in Tetany,

(*Footnote continued on page 860*)

EXPERIMENTAL WORK

In the experimental work reported here, time curves have been obtained on the influence of the ingestion of sweet milk, acidified milk and a number of calcium salts and the effect of the injection of parathyroid extract on the total calcium, diffusible calcium, nondiffusible calcium and inorganic phosphate of the blood serum. The experimental methods used in the analyses have been described by us.[2b] The experiments were carried out on both human subjects and dogs. The human subjects were medical students of both sexes. Rather large dogs were selected for the work. Throughout, the dogs were fed on a diet of bread and meat, with the addition of an occasional small portion of cod liver oil. The last meal before an experiment was carried out was taken on the evening previous to the experimental period; during the course of the experiment no food was allowed, but water was permitted *ad libitum*. The data are given in the form of graphs from representative experimental results obtained for the particular experimental procedure.

Effect of Short Periods of Fasting.—The calcium changes of the blood in animals and man over prolonged periods of starvation have been studied by a considerable number of authors, among whom may be mentioned Cavins,[18] Morgulis,[19] Morgulis and Perley,[20] Farquharson and Tibbetts[21] and Lennox, O'Connor and Bellinger.[22] The net result of the work on this subject is that in starvation the calcium and inorganic phosphate undergo little change until an advanced stage of inanition is reached. However, in the experiments cited, blood was drawn and analyses were carried out only at intervals of several days

J. Clin. Investigation **5**:259 and 277 (Feb.) 1928. Reed, C. I.: On the State of Plasma Calcium in Parathyroidectomized Dogs, J. Biol. Chem. **77**:547 (May) 1928. Greene, C. H., and Power, M. H.: Distribution of Electrolytes Between Serum and in Vivo Dialysate, ibid. **91**:183 (April) 1931. Brown, H., and Ramsdell, S. G.: Blood Calcium Distribution in Anaphylaxis in Guinea Pig, J. Exper. Med. **49**:705 (May) 1929. McCance, R. A., and Watchorn, E.: Inorganic Constituents of Cerebrospinal Fluid: Calcium and Magnesium, Quart. J. Med. **24**:371 (April) 1931.

18. Cavins, A. W.: Effect of Fasting (and Refeeding) on Calcium and Inorganic Phosphorus in Blood Serums of Normal and Rachitic Cats, J. Biol. Chem. **59**:237 (Feb.) 1924.

19. Morgulis, S.: Chemical Changes in Blood During Fasting and Subsequent Re-Feeding: Inorganic Components, Am. J. Physiol. **84**:350 (March) 1928.

20. Morgulis, S., and Perley, A. M.: Changes in Serum Calcium of Cats During Fasting, Am. J. Physiol. **89**:213 (June) 1929.

21. Farquharson, R. F., and Tibbetts, D. M.: Studies of Calcium and Phosphorus Metabolism: On Temporary Fluctuations in Level of Calcium and Inorganic Phosphorus in Blood Serum of Normal Individuals, J. Clin. Investigation **10**:271 (June) 1931.

22. Lennox, W. G.; O'Connor, M., and Bellinger, M.: Chemical Changes in the Blood During Fasting in the Human Subject, Arch. Int. Med. **38**:553 (Nov.) 1926.

or longer, and so do not rule out the possibility that a daily cycle of change may be present in the calcium fractions and phosphate, perhaps dependent on the daily rhythm of the activities and habits of the subject. Such a cycle of changes, if it existed, would have a considerable bearing on any experiments designed to determine the effects of agents influencing blood calcium. Accordingly, a series of determinations was carried out on human subjects and dogs undergoing short fasting periods to detect such daily changes if they exist.

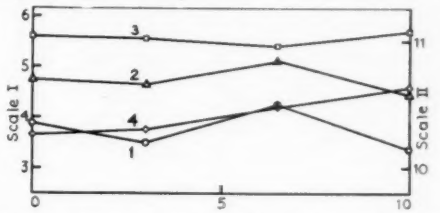

Chart 1.—This experiment on a human subject (W) shows practically no fluctuation in calcium but a definite increase in inorganic serum phosphate of about 1 mm. during a short period of fasting. In all of these charts (except chart 5) the magnitude of the total calcium is given by scale *II* on the ordinate on the right side of the drawing, while the amounts of diffusible calcium, nondiffusible calcium and inorganic serum phosphate are represented on scale *I* on the left side of the drawing. The abscissa measures the time in hours. In all cases, the curves for total calcium are numbered *1* and the experimental points are represented by the circles; the curves for diffusible calcium are numbered *2* and the points are shown by the triangles; curve *3* and the squares represent the nondiffusible calcium; the inorganic serum phosphate curves are numbered *4* and the experimental points are marked with the diamond-shaped symbols.

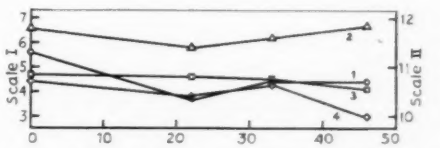

Chart 2.—A short fasting period in a dog (dog 8, weighing 15 Kg.) produces a small drop in calcium from the initial value with erratic changes in the inorganic serum phosphate.

In these experiments, food was last taken on the evening before the day of the experiment; the first sample of blood was drawn at about 8 a. m. the next day, and other samples of blood at varying intervals during the day. Curves, illustrating the kind of results obtained, are shown in chart 1 for a human subject, and in chart 2 for a dog. The curves, which are typical, show that there is a trend toward a small drop in the total calcium from the initial value. This small drop in the beginning may perhaps be taken to indicate that there ordinarily exists a

slight plethora of calcium which is brought down to a constant stable level soon after the start of the fasting period. This drop seems to be due to fluctuations in the diffusible calcium with almost no change in nondiffusible calcium. However, as the figures here are bordering on the limits of error of the analytic methods, a clearcut decision cannot be made. The changes of the inorganic phosphate during the fasting period were somewhat erratic, showing no well defined tendency.

These experiments rule out the possibility of daily rhythms taking place in the calcium and inorganic phosphate of sufficient magnitude to be important in obscuring the results of agencies that have an effect on blood calcium.

Effect of Ingestion of Milk.—Milk is an important source of calcium for the whole of the animal kingdom. Furthermore, it has been shown that parathyroid-deficient animals fed on a milk diet can be kept free from tetanic symptoms.[23] Salvesen[24] has shown that this favorable influence of milk in parathyroprivia is due to nothing else than its calcium content, calcium-free milk being ineffectual in this respect. From this, it readily follows that a study of the effect of the ingestion of milk on the calcium and phosphate content of the blood is of great interest, and accordingly was undertaken by us.

The experiments with milk were all carried out on human subjects. Without eating any breakfast, the subject drank 1 liter of milk at about 8 a. m. This amount of cow's milk contains about 1.2 Gm. of calcium and 0.93 Gm. of phosphorus.[25] A sample of blood to serve as a control was drawn immediately before the ingestion of milk and then further samples of blood were taken at varying intervals during the day. Two kinds of milk were employed in the experiment, pasteurized sweet milk and acidified milk prepared with lactic acid.[26]

Differences in the results were obtained with the two kinds of milk. With sweet milk there were no regular changes produced in serum calcium, while an increase took place in the inorganic phosphate, as is

23. Dragstedt, L. R., and Peacock, S. C.: Pathogenesis of Tetany: Control and Cure of Parathyroid Tetany by Diet, Am. J. Physiol. **64**:424 (May) 1923. Inouye, T.: Experimental Tetany and Diet, ibid. **70**:524 (Nov.) 1924.

24. Salvesen, H. S.: Studies on Physiology of Parathyroids, Acta med. Scandinav., 1923-1924, supp. 6.

25. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 3, New York, The Macmillan Company, 1925, p. 590.

26. The acidified milk was prepared by the pediatrics department of the University of California Medical School according to the following formula: One hundred cubic centimeters of karo syrup is added to 1 liter of fresh milk, and the whole mixed thoroughly. The milk is then heated to boiling for three minutes and again cooled in an ice chest. When cold, 20 cc. of 85 per cent lactic acid is added, drop by drop, the milk being vigorously stirred during the procedure.

shown in chart 3. In some instances there were small increases (chart 3 *A*), and in others decreases (chart 3 *B*), of the total calcium amounting to several tenths of a milligram per hundred cubic centimeters. This was due to changes in the diffusible rather than the nondiffusible calcium. The changes in inorganic phosphate were not always constant, although most often there was an increase. The increase in the phosphate was about 1 mg. per hundred cubic centimeters over a period of eight hours.

With acidified milk, on the contrary, a quite different picture was obtained. On this regimen, the calcium increased ordinarily by about 1 mg. per hundred cubic centimeters, the whole of the increase again being in the diffusible fraction while the nondiffusible fraction remained constant, as is shown in chart 4. Along with the increase in the calcium there was an increase in inorganic phosphate, also to the value of about

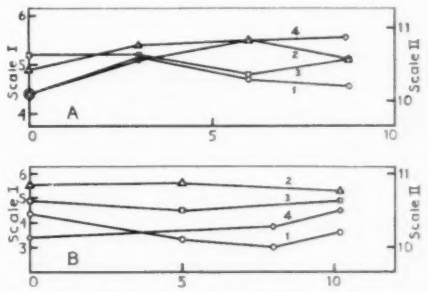

Chart 3.—*A*, the effect of the ingestion of 1 liter of sweet milk (subject L.), showing small erratic fluctuations in the calcium and an increase of about 1 mg. per hundred cubic centimeters in the inorganic phosphate over an eight hour period. *B*, this experiment on the ingestion of sweet milk (subject S.) shows a small drop in the calcium and, as in *A*, an increase in the phosphate.

1 mg. per hundred cubic centimeters of serum. In both the calcium and the phosphate the maximum of the increase occurred about eight hours after the ingestion of the milk.

How is the difference in the behavior between the two types of milk to be explained? The explanation that seems plausible to us is that the height of the blood calcium after the ingestion of a calcium compound depends on a balance between absorption and the factors that make for the removal of calcium, such as excretion and deposition as bone and tissue calcium. On this reasoning, only when there is a marked excess of absorption is there a rise in the calcium level. Ordinary sweet milk does not favor a rapid absorption, since the balance between acid and basic radicals is such that a large part of the calcium is precipitated in the intestinal tract. On the other hand, acidified milk with its excessive acid content favors a greater content of soluble calcium

in the intestinal tract, and other things being equal, this would favor absorption and tend to increase the level of blood calcium.

Effect of Ingestion of Calcium Salts.—The influence of ingested calcium salts on the blood calcium has been extensively investigated. Until only a few years ago, many of the workers on this subject reported that they were unable to increase the level of the blood calcium by the feeding of calcium salts. Among this group of authors were Meigs, Blatherwick and Carey,[27] Denis and Corley,[28] Halverson, Mohler and Bergeim,[29] Clark [30] and Salvesen, Hastings and McIntosh.[31]

In the light of present-day knowledge it seems probable that this group of workers missed the increase in the blood calcium because of

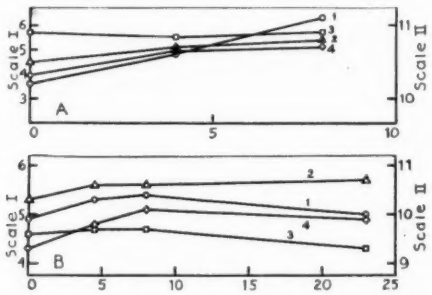

Chart 4.—*A*, with the ingestion of 1 liter of acid milk (subject G), there is an increase of about 1 mg. per hundred cubic centimeters in the serum calcium and also an increase in the inorganic phosphate as with sweet milk. It is to be noted that the increase in calcium is caused solely by an increase of the diffusible calcium. *B*, another experiment with acid milk (subject T), showing more definitely that the maximum of the calcium and phosphate increase comes about eight hours after ingestion of the milk.

shortcomings in the experimental procedure, the chief ones being failure to draw samples of blood at the right intervals and allowing the partaking of food during the experiments.

27. Meigs, E. B.; Blatherwick, N. R., and Carey, C. A.: Contributions to the Physiology of Phosphorus and Calcium Metabolism as Related to Milk Secretion, J. Biol. Chem. **37**:1 (Jan.) 1919.

28. Denis, W., and Corley, R. C.: Study of Effect of Excessive Calcium Ingestion on the Calcium Content of Tissues With and Without the Application of Ultra-Violet Light, J. Biol. Chem. **66**:609 (Dec.) 1925.

29. Halverson, J. O.; Mohler, H. H., and Bergeim, O.: Calcium Content of Blood Serum in Certain Pathological Conditions, J. Biol. Chem. **32**:171 (Nov.) 1917.

30. Clark, G. W.: Effect of Hypodermic and Oral Administration of Calcium Salts on Calcium Content of Rabbit Blood, J. Biol. Chem. **43**:89 (Aug.) 1920.

31. Salvesen, H. A.; Hastings, A. B., and McIntosh, J. F.: Effect of Administration of Calcium Salts on Inorganic Composition of Blood, J. Biol. Chem. **60**: 327 (June) 1924.

It has been conclusively shown that, when properly carried out, the ingestion of a soluble calcium salt produces an increase in blood calcium. The salts that have been most extensively employed have been calcium chloride, calcium lactate and, recently, calcium gluconate. From among the many studies may be cited those of Mason,[32] Blum, Aubel and Hausknecht,[33] Stewart and Haldane [34] and Lasch and Neumayer [35] on calcium chloride, those of Luckhardt and Goldberg,[36] Kahn and Roe,[37]

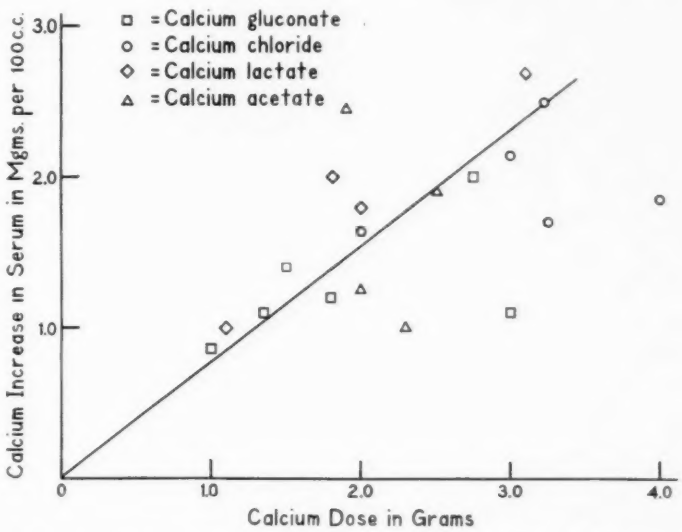

Chart 5.—Plot of the increase in the serum calcium obtained in dogs after the oral ingestion of the salts listed in the drawing which indicates that the increase in calcium is proportional to the calcium content of the dose and is independent of the particular calcium salt employed.

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32. Mason, E. H.: Absorption of Calcium Salts in Man, J. Biol. Chem. **47**:3 (June) 1921.

33. Blum, L.; Aubel, E., and Hausknecht, R.: Modification de la composition minérale du sang et des humeurs aprés ingestion de chlorure de calcium, Compt. rend. Soc. de biol. **85**:1159, 1921.

34. Stewart, C. P., and Haldane, J. B. S.: Experimental Alterations in the Calcium Content of Human Serum and Urine, Biochem. J. **18**:855, 1924.

35. Lasch, F., and Neumayer, K.: Resorption of Calcium in Peroral Administration, Biochem. Ztschr. **174**:333, 1926.

36. Luckhardt, A. B., and Goldberg, B.: Preservation of the Life of Completely Parathyroidectomized Dogs, J. A. M. A. **80**:79 (Jan. 13) 1923.

37 Kahn, B. S., and Roe, J. H.: Calcium Absorption from the Intestinal Tract in Human Subjects, J. A. M. A. **86**:1761 (June 5) 1926.

Bauer and Ropes [38] and Hoyle [39] on calcium lactate, those of Rothlin [40] and Liebermann [41] on calcium gluconate and those of Jansen [42] and Hjort [43] on a number of calcium salts.

The most extensive series of such experiments is that of Hjort. The typical results according to his findings are: If the salt is administered on an empty stomach and in sufficient dosage, there is an increase in the serum calcium which reaches a maximum in about two hours and then drops back to the preingestion level in about four hours. This sequence of events is in agreement with the experience of most of the authors mentioned.

The amount of the increase obtained is a matter of some dispute. Kahn and Roe [37] claimed an elevation of 80 per cent in human subjects given 20 Gm. of calcium lactate. Bauer and Ropes [38] took exception to Kahn and Roe's figure and stated that there is an average elevation of only about 15 per cent with 10 Gm. doses of calcium lactate. Hoyle [39] obtained an increase of from 10 to 15 per cent in serum calcium in rabbits given doses of 3 Gm. of calcium lactate per kilogram. Liebermann [41] obtained increases of around 70 per cent with doses of 10 Gm. of calcium gluconate fed to young human adults, although he stated that the results varied greatly with the individual. Working with dogs, Hjort [43] found an increase in serum calcium with calcium chloride, calcium lactate and calcium glycerophosphate when the dosage was greater than 0.195 Gm. of calcium per kilogram of body weight. With calcium lactate at a level of 1.5 Gm. per kilogram, Hjort obtained an average increase of about 40 per cent. It is also commonly held that calcium chloride is superior to other salts in increasing the level of serum calcium because of its acidotic effect.[44]

Since all the investigations cited suffer from the defect that there has been considered only the change produced in the total calcium of

38. Bauer, W., and Ropes, M. W.: Effect of Calcium Lactate Ingestion on Serum Calcium, J. A. M. A. **87**:1902 (Dec. 4) 1926.

39. Hoyle, J. C.: Studies in Serum Calcium: Oral Administration, J. Pharmacol. & Exper. Therap. **32**:309, 1928.

40. Rothlin, E.: Experimentelle Untersuchungen über Resorption und Wirkungsweise des gluconsauren Calciums, Ztschr. f. d. ges. exper. Med. **70**:634, 1930.

41. Liebermann, A. L.: Studies on Calcium: Blood Calcium Changes Following Administration of Calcium Gluconate Given Subcutaneously to Normal and Parathyroidectomized Dogs and per Os to Human Beings, J. Pharmacol. & Exper. Therap. **42**:245 (June) 1931.

42. Jansen, W. H.: Kalkstoffwechsel, Blutkalkgetralt und Kalkwirkung, Klin. Wchnschr. **3**:715, 1924.

43. Hjort, A. M.: Influence of Orally Administered Calcium Salts on Serum Calcium of Normal and Thyreoparathyroprivic Dogs, J. Biol. Chem. **65**:783 (Oct.) 1925.

44. Stewart, C. P., and Percival, G. H.: Calcium Metabolism, Physiol. Rev. **8**:283, 1928.

the serum as a result of the ingestion of calcium salts, we have carried out a series of experiments to obtain the time curves for the diffusible calcium, nondiffusible calcium and inorganic phosphate as well, using both human subjects and dogs for the experiments. The experimental procedure was much the same as for the experiments on the ingestion of milk, the calcium salts being given with liberal quantities of water. The results that were obtained are illustrated by the curves given in charts 6 to 10, in which there are plotted the data of representative experiments for each of the calcium salts employed. In these curves there are shown the changes in total calcium, diffusible calcium, nondiffusible calcium and inorganic serum phosphate after the ingestion of a calcium salt. To economize space, only the results obtained on dogs are included here, since the results on the human subjects are quite similar.

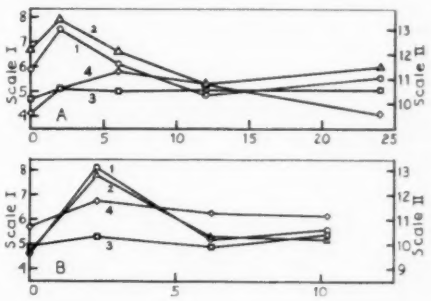

Chart 6.—*A*, curves for calcium fractions and inorganic phosphate fractions after ingestion of 7 Gm. of calcium chloride (dog E, weighing 14 Kg.). The chart shows the features usually obtained, an increase in serum calcium with a maximum at about two hours, which is due solely to the increase in the diffusible calcium, the nondiffusible calcium remaining within experimental error unaltered during the experiment. The inorganic serum phosphate also increases and reaches a maximum in about six hours. *B*, another experiment with calcium chloride (12 Gm.), showing the usual features except that the phosphate maximum is reached in two hours (dog 2, weighing 17 Kg.).

Our results for the change in total serum calcium agree with the sequence of events obtained by Hjort. If no emesis or diarrhea occurred, there was produced a considerable increase in serum calcium, the maximum ordinarily coming about two hours after the ingestion of the salt. We were, however, unable to confirm the point of view that there are exceptional differences in the efficiency of effect among the soluble calcium salts that we employed, including calcium chloride. Rather, the observations are in better harmony with the view that the increase in blood calcium is proportional to the calcium content of the

dose employed, irrespective of which salt is employed. This is graphically shown by chart 5, in which there are plotted the maximal increases in the total serum calcium obtained in the experiments with dogs with calcium chloride, acetate, lactate and gluconate. In this chart the maximum increase obtained in serum calcium, in milligrams per hundred cubic centimeters, for each experiment is plotted against the calcium content of the dose of the salt employed. While there is a considerable scattering of some of the points, the general trend favors a proportionality between the level of increase and calcium dosage not dependent on the particular salt. The line drawn through the points in the charts shows that with a dose of calcium of 2 Gm., which corresponds to about

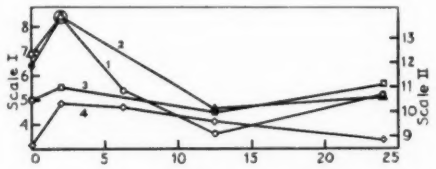

Chart 7.—An experiment with calcium lactate (10 Gm.) showing the same features as were obtained with calcium chloride (dog B, weighing 13.5 Kg.).

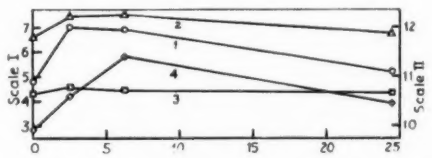

Chart 8.—The results obtained on the ingestion of 15 Gm. of calcium gluconate (dog 4, weighing 22 Kg.), again illustrating that the increase in the serum calcium is due solely to an increase in the diffusible calcium while the nondiffusible calcium remains unaltered. The results show the typical features of the maximum of the calcium increase at two hours and the maximum of the phosphate increase at six hours.

7 Gm. of calcium chloride, 8 Gm. of calcium acetate, 11 Gm. of calcium lactate and 22 Gm. of calcium gluconate, there was obtained an average increase of 1.5 mg. per hundred cubic centimeters, which represents approximately a 15 per cent increase in serum calcium. While the response is largely dependent on the dose of calcium, our results agree better with the authors who report only moderate increases in serum calcium.

It is of great interest and particularly to be noted that the change in the serum calcium is a result of the change in the diffusible calcium which mirrors the change in total calcium almost exactly, while the non-

diffusible calcium, except for what are probably experimental errors, remains unchanged throughout the whole cycle of events. The whole of the absorbed calcium which determines the increase in the blood calcium level over this period of about four hours remains in a diffusible condition, undergoing no reaction with the plasma proteins to become partially converted to the nondiffusible calcium. From what was stated in the introduction, it follows that all this extra calcium should be expected to remain physiologically active.

The behavior of the inorganic serum phosphate is another point of great interest. Along with the change in calcium there takes place a

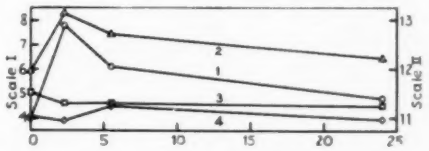

Chart 9.—Another experiment with calcium gluconate (16.5 Gm.) in which the serum calcium increase was greater (dog 4, weighing 22 Kg.). The chart confirms the typical response in the calcium fractions found on the ingestion of calcium salts.

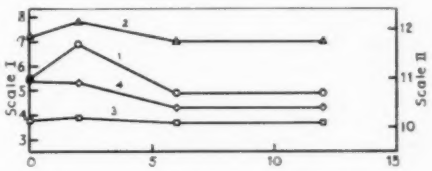

Chart 10.—An experiment with calcium acetate (6 Gm.), showing the usual features obtained with the other calcium salts except for a drop in the inorganic phosphate (dog L, weighing 20 Kg.).

characteristic sequence of change in the serum phosphate. The phosphate increases along with the calcium, usually to a value of about 1 mg. per hundred cubic centimeters. The sequence of change, however, does not coincide with that of the calcium, since the increase is maintained for a much longer period, lasting about six hours and then slowly falling back to the initial value.

Effect of the Injection of Parathyroid Extract.—In 1925, Collip announced the isolation of a potent extract from beef parathyroid glands with the power of being able strongly to increase the level of the serum calcium in parathyroprival and in normal animals. Since the announcement, the biochemical influence of Collip's and other similar extracts has

been extensively studied by Collip and his collaborators [45] and by other workers.[46]

The majority of the studies have been concerned with the change in total serum calcium only, but unlike those studying other calcium-influencing agencies, several authors have investigated the changes undergone by the diffusible and nondiffusible calcium; among these are Moritz,[46d] working on rabbits, and Snell,[46e] working on dogs. When the present work was undertaken, Snell's paper had not yet been published and only Moritz' studies were available. Since there are a number of objections to using rabbits as subjects for studies of blood calcium because of their marked insensitivity to factors affecting the blood calcium, and since Moritz' experiments show only small increases in the serum calcium, experiments were planned and carried out on the effect of injections of parathyroid extract on the total calcium, diffusible calcium, nondiffusible calcium and inorganic phosphate of serum, using dogs as experimental subjects. The time curves of representative results with single doses of parathyroid extract are given in chart 11 *A* and *B*, and the curves for the effect of a repeated dose are shown in chart 11 *C*. For these experiments, Collip's parathyroid extract was used, the injections being given subcutaneously.

On injecting a single dose of from 100 to 200 units of parathyroid extract-Collip, the maximum of the increase was found to be at about the twenty-fourth hour. This is not in agreement with Collip, Clark and Scott,[45a] who stated that the maximum level under such conditions is obtained in from five to nine hours. Furthermore, the return to the normal calcium values in our experiments required about seventy-two hours as against about fifteen hours found by Collip, Clark and Scott. Just what the reasons are for the differences in the behavior between our animals and those of Collip, Clark and Scott we are at a loss to explain. In only two instances in fifteen experiments carried out was

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45. (*a*) Collip, J. B.; Clark, E. P., and Scott: Effect of a Parathyroid Hormone on Normal Animals, J. Biol. Chem. **63**:439 (March) 1925. (*b*) Collip, J. B.: The Parathyroid Glands, Medicine **5**:1 (Feb.) 1926.

46. (*a*) Albright, F.; Bauer, W.; Ropes, M., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: Effect of Parathyroid Hormone, J. Clin. Investigation **7**:139, 1929. (*b*) Hjort, A. M.; Robison, S. C., and Tendick, F. H.: Extract Obtained from External Bovine Parathyroid Glands Capable of Inducing Hypercalcemia in Normal and Parathyroprivic Dogs, J. Biol. Chem. **65**:117 (Aug.) 1925. (*c*) Berman, L.: Effect of Protein-Free Acid-Alcohol Extract of Parathyroid Glands upon Calcium Content of Blood and Electrical Irritability of Nerves of Parathyroidectomized and Normal Animals, Am. J. Physiol. **75**:358 (Jan.) 1926. (*d*) Moritz, A. R.: State of Serum Calcium in Experimental Hypo- and Hypercalcemia, J. Biol. Chem. **66**:343 (Dec.) 1925. (*e*) Snell, A. M.: Diffusibility of Calcium in Blood Serum Under Normal and Pathological Conditions, Proc. Staff Meet., Mayo Clin. **5**:17 (Jan. 22) 1930.

the maximum increase obtained in less than twenty-four hours, one of these two exceptions occurring at six hours and the other at thirteen hours.

Of marked interest are the curves for the diffusible and nondiffusible calcium. When the blood calcium level is increased by an injection of parathyroid extract, the increase is reflected in both the diffusible and the nondiffusible fractions, while, as shown, when the increase is produced by a calcium-containing compound, the increase takes place only in the diffusible calcium. The increase in both fractions of the calcium after the injection of parathyroid extract-Collip agrees with the findings of

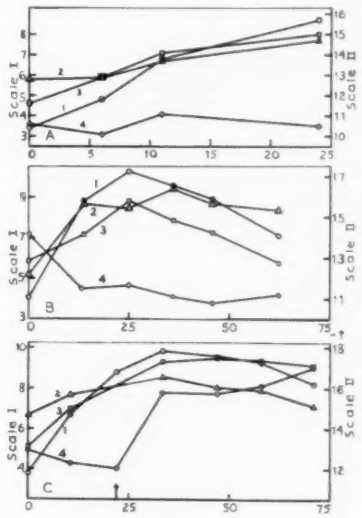

Chart 11.—*A*, changes in the calcium fractions and inorganic serum phosphate after the injection of 100 units of parathyroid extract-Collip (dog 3, weighing 15 Kg.), showing the continual increase in calcium up to twenty-four hours. The increase is about equally divided between diffusible and nondiffusible calcium. The drop in the inorganic serum phosphate is not as pronounced as is usually the case. *B*, effect of the injection of 150 units of parathyroid extract-Collip (dog 4, weighing 25 Kg.), showing the added response for the extra amount of parathyroid extract. The chart illustrates the significant features of the maximum of response in about twenty-four hours, the slow return to normal, the distribution of the increase in calcium about equally between the diffusible and nondiffusible calcium and the drop in inorganic serum phosphate as the calcium increases. *C*, effect of the injection of a repeated dose of parathyroid extract-Collip (dog B, weighing 22 Kg.). Each of the two doses consisted of 100 units; the time of the injection of the second dose is indicated by the arrow. The effect on calcium noted here is little different from that of a single injection, except for the prolongation in the time of the increased serum calcium. After the second injection the inorganic phosphate shows the increase that is associated with an overdose of parathyroid extract.

Moritz [46d] and Snell.[46e] The increased calcium is about equally divided between the two fractions. This is readily seen in the charts. When a second dose of the extract is given before the calcium returns to its initial value, the serum calcium goes to still higher levels, as has been shown by Collip, Clark and Scott. In chart 11 *C* are given the curves for the effect of a repeated dose of parathyroid extract. These show that the extra increase in total calcium is also distributed between diffusible and nondiffusible calcium. With a repeated dose, it is seen that the calcium level remains heightened for a considerably longer time than with a single dose.

The behavior of the serum inorganic phosphate is no less interesting than that of the diffusible and nondiffusible calcium fractions. When

TABLE 2.—*The Effect of Repeated Injections of Parathyroid Extract-Collip, Long Intervals Apart, in Dog 3* *

		Initial Values				Time of Maximum Increase, Hrs.	Maximum Values			
Date	Dose, Units	Total Calcium	Diffusible Calcium	Nondiffusible Calcium	Phosphorus		Total Calcium	Diffusible Calcium	Nondiffusible Calcium	Phosphorus
Jan. 14	100	10.4	5.80	4.60	3.55	24	15.70	7.70	8.00	3.50
Feb. 15	100	11.6	6.10	5.50	4.75	25	15.80	7.80	8.00	3.30
Feb. 25	200	10.7	6.10	4.60	4.75	24	16.80	8.40	8.40	2.90
April 5	150	11.8	5.60	6.20	4.15	35	17.80	9.00	8.80	4.65
April 22	150	10.8	6.20	4.60	3.70	13	14.70	8.70	6.00	3.10

* Analytic figures in milligrams per hundred cubic centimeters of serum.

an increase in blood calcium was produced by the administration of a calcium salt, there was found a concomitant increase in inorganic serum phosphate which persisted even longer than the increased calcium level. When the blood calcium was increased by the injection of from 100 to 200 units of parathyroid extract-Collip the serum phosphate did not increase. Instead, it dropped, as is shown in the charts. A drop of this type is to be noted in some of the curves given by Collip [45b] but without comment. This observation has also been made and extensively discussed by Albright, Bauer, Ropes and Aub [46a] and by Albright, Bauer, Cockrill and Ellsworth.[47] The extent of the drop in the phosphate, it is to be noted, depends on its initial value. When this is high, as in experiment 15, in which it was a little over 7 mg. per hundred cubic centimeters, the drop is considerable—to 4.5 mg. per hundred cubic centimeters. With initially low values of serum phosphate, the drop is small

47. Albright, F.; Bauer, W.; Cockrill, J. R., and Ellsworth, R.: Studies on Physiology of Parathyroid Glands: Relation of Serum Calcium to Serum Phosphate at Different Levels of Parathyroid Activity, J. Clin. Investigation **9**:659 (Feb.) 1931.

or may even be absent. Albright, Bauer, Ropes and Aub [45a] stated that when the serum calcium rises above a critical level of about 15 mg., the blood phosphorus rises. With dogs we did not find this to be so, when the drop persisted at values of over 17 mg. per hundred cubic centimeters. However, when a repeated dose of parathyroid extract-Collip was given, as in the experiment recorded in chart 11 *C*, a rise of the phosphate did take place. This rise in phosphate has been thoroughly discussed by Collip [45b] as an important factor in the phenomenon of overdosage with parathyroid extract discovered by him.

The effect of the periodic injection of doses of parathyroid extract-Collip is of interest. The results of such a series carried out at various intervals during a three month period are given in table 2. The table shows no particularly persistent influence of the repeated injections over the periods in which the parathyroid extract was given.

In some of the periods the response does not appear to be proportional to the dosage of parathyroid extract, but it is not possible from these results to argue justifiably that there is an increasing loss of susceptibility to the parathyroid extract with the repeated injections when there is a lapse of several weeks between each injection.

COMMENT

The most significant observations in the experimental work are the contrasts in the effects produced when the level of the blood calcium is increased by a calcium-containing compound and by the injection of parathyroid extract-Collip. With a soluble calcium compound, the increase is solely in the diffusible calcium fraction and there is a concomitant increase in inorganic serum phosphate, while when the calcium increase is induced by parathyroid extract the two calcium fractions both share in the increase and the inorganic serum phosphate decreases. These observations show that the actual mechanism of the factors governing the interrelation of diffusible calcium, nondiffusible calcium and inorganic phosphate of the blood in vivo is more complex than the picture outlined in the introduction.

It might be pointed out that so far nothing has been said of the changes undergone by the serum proteins during these experiments; if they were taken into account, the results would perhaps fit better into the mechanism just mentioned. Actually, such is not the case. Serum proteins were determined in many of the experiments by the method of one of us (Dr. Greenberg [48]), and the proteins, including both the albumin and the globulin, were found to remain unchanged throughout the course of an experiment. One point that may be an important factor in the difference in behavior is the time. The changes in calcium are over

48. Greenberg, D. M.: Colorimetric Determination of Serum Proteins, J. Biol. Chem. **82**:545 (May) 1929.

within about four hours after the ingestion of a calcium salt, and they only reach their maximum twenty-four hours after the injection of parathyroid extract-Collip.

Little more can be said than this at present concerning the nature of the different behavior. The action of parathyroid extract fits in well with the mechanism pictured in the introduction. As the blood calcium increases, the increase is distributed according to some equilibrium between diffusible and nondiffusible calcium, the level of the nondiffusible calcium being determined by the serum protein content. Also, with an increase in diffusible calcium, if the solubility product of a calcium salt determines the relation between the calcium and the phosphate ion, the inorganic serum phosphate should decrease, as it actually is found to do.

On the contrary, the changes observed after the ingestion of a calcium salt are at present unexplainable on the hypothesis laid down in the introduction, unless the duration of the increase in calcium is too short a period to allow an equilibrium between diffusible calcium and inorganic phosphate and diffusible calcium and nondiffusible calcium to be established. Otherwise, it does not seem possible to reconcile the fact that only the diffusible calcium increases, while the inorganic phosphate content, instead of decreasing, rises, with the current theories of the mechanism that determines the level of blood calcium.

SUMMARY

1. An experimental study has been carried out on the changes produced in the diffusible calcium, nondiffusible calcium and inorganic phosphate of the serum by certain agents that are capable of affecting the level of the blood calcium.

2. Criticisms directed against the determination of diffusible calcium have been considered, and it is pointed out that the method used by us has given reproducible and concordant results, not only in our own hands, but in the hands of many investigators in widely separated laboratories.

3. In a dog with a bile-renal fistula in which there was complete elimination of bile from the body, there was found to be little change in total and diffusible calcium during a period of about two months, contrary to the claims made by Emerson.[14]

4. During short periods of fasting, no marked changes were found to take place in the calcium and inorganic phosphate of the serum, indicating that there is no daily rhythm of change in the calcium fractions and phosphate of the blood.

5. In experiments on the ingestion of milk by human subjects, marked differences in the effect produced were found between sweet and acidified milk. When 1 liter of sweet milk was ingested, no increase

took place in the blood calcium—in fact, there was usually a slight decrease. The inorganic serum phosphate in these experiments ordinarily increased. With the ingestion of 1 liter of acidified milk, on the other hand, an increase took place in both the calcium and the phosphate, the maximum of the increase coming about eight hours after the ingestion of the milk. The increase amounted to about 1 mg. of calcium per hundred cubic centimeters of serum, and was due to an increase in the diffusible fraction, the nondiffusible calcium remaining unchanged.

6. The increase of the serum calcium in dogs on the oral ingestion of calcium chloride, lactate, acetate and gluconate was found to be the same for all of these salts, when given in equivalent quantities. The increase in calcium was found to be proportional to the calcium content of the dose of the salt. No special efficacy in increasing blood calcium was found with any of these calcium salts.

7. When the blood calcium was increased by the ingestion of calcium, chloride, lactate, acetate or gluconate, the maximum of the increase occurred about two hours, and the blood calcium returned to the initial value in about four hours, after the ingestion of the salt. The inorganic serum phosphate also increased, the increase being about 1 mg. per hundred cubic centimeters, regardless of the dose of calcium. The maximum increase in phosphate came after the calcium content had dropped to normal, namely, in about six hours.

The total increase in the serum calcium after the ingestion of a calcium salt is due to an increase in the diffusible calcium fraction alone, while the nondiffusible calcium remains unaltered throughout the experiment.

8. When single doses of parathyroid extract-Collip of from 100 to 200 units were injected subcutaneously into dogs weighing from 15 to 25 Kg., the increase in serum calcium was found to require about twenty-four hours to reach the maximum and about seventy-two hours to fall back to the initial value. With parathyroid extract-Collip the increase in calcium was found to be due to an increase in both the diffusible and the nondiffusible fractions, the amount of the increase being about equally divided between the two fractions. The inorganic serum phosphate in these experiments showed a drop from the initial values. When a repeated dose of parathyroid extract-Collip is given at about the point of the maximum of the first, the extra increase in calcium has about the same features as for a single dose.

CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS MONKEYS

VI. THE BROMSULPHALEIN LIVER FUNCTION TEST AND THE VAN DEN BERGH REACTION

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AND
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In previous articles [1] it has been shown that there is a definite decline in hepatic function during the course of yellow fever. This loss of function makes itself evident about twenty-four hours before death (in some cases earlier), through alterations in the fasting blood sugar and in the blood sugar curves following the injection of dextrose. In the later stages of the disease, usually during the last ten or twelve hours before death, there are marked changes in the nitrogen metabolism and in some of the mineral elements of the blood and the urine.

In this paper are presented the results of further tests for hepatic function: (1) the bromsulphalein liver function test, (2) determination of the bilirubin content of blood by the van den Bergh reaction and (3) a number of examinations made for fibrin and the coagulation time of the blood. The bromsulphalein liver function test was performed by the technic described by Rosenthal and White.[2] Five milligrams of the dye per kilogram of body weight was injected intravenously. The bilirubin content of the blood was determined by the van den Bergh reaction as described by McNee.[3] The coagulation time of the blood was determined by Lee and White's method.[4] The fibrinogen in the

From the laboratory of the West African Yellow Fever Commission of the International Health Division, Rockefeller Foundation, Lagos, Nigeria.

1. Wakeman, A. M., and Morrell, C. A.: (*a*) Chemistry and Metabolism in Experimental Yellow Fever: I. Concentration of Nonprotein Nitrogenous Constituents in the Blood, Arch. Int. Med. **46**:290 (Aug.) 1930; (*b*) II. Nitrogen Metabolism, ibid. **46**:382 (Sept.) 1930; (*c*) III. Blood Sugar and Liver Glycogen, ibid. **47**:104 (Jan.) 1931; (*d*) IV. Tolerance Tests for Dextrose, ibid. **48**:301 (Aug.) 1931; (*e*) V. Acid-Base and Electrolyte Equilibrium, ibid. **49**:826 (May) 1932.

2. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112 (April 11) 1925.

3. McNee, J. W.: Jaundice: Review of Recent Work, Quart. J. Med. **16**:390 (July) 1923.

4. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1927, p. 228.

plasma was estimated from the difference between the protein content before and after the removal of fibrinogen with calcium chloride.[5]

EXPERIMENTAL METHODS

1. *Van den Bergh Determinations.*—Chart 1 presents the results of forty-nine determinations of bilirubin. Four of these were made on normal monkeys and the remainder on monkeys in various stages of

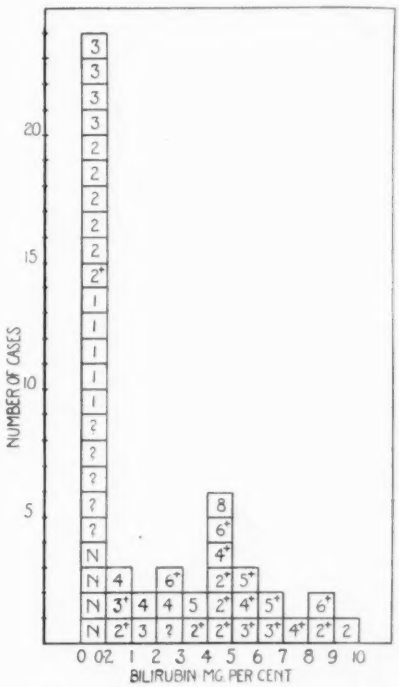

Chart 1.—Blood bilirubin in yellow fever. The number in a square indicates the day of fever on which the sample of blood was taken. A question mark signifies that the day of fever is unknown. *N* signifies a normal monkey. + signifies that the monkey died within ten hours after the sample of blood was taken.

yellow fever. Monkeys with only a trace (up to 0.2 mg. per hundred cubic centimeters) of bilirubin in the serum are presented in the first column. This column includes figures obtained from normal monkeys; the majority of the remainder are from animals in the early stages of

5. Hawk, P. B., and Bergeim, Olaf: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1927, p. 398.

yellow fever. One animal died on the second day of fever with less than 0.2 mg. of bilirubin per hundred cubic centimeters of blood. The course of illness in this animal was short. Death occurred on the third day after inoculation, when the blood serum contained 15.7 mg. of inorganic phosphorus and 94 per cent of nonprotein nitrogen, and when the blood sugar was only 25 mg. These abnormalities suggest a considerable loss in hepatic function.[6] Two other monkeys died with a serum bilirubin content of less than 1 mg. Only 15 per cent of the animals (five of thirty-four) died with a van den Bergh value of less than 4 mg.

No correlation was observed between the length of the febrile period and the degree of jaundice. In four cases, monkeys in the third day of fever had no more than a trace of pigment in the serum, while the monkey showing the highest amount of pigment in the serum was in the second day of fever.

2. *Bromsulphalein Liver Function Tests.*—Dye was injected into twelve monkeys. Three of these were normal monkeys that were not later infected with yellow fever. Several animals were given injections on consecutive days of the disease, and alterations in their ability to excrete the dye were noted. Results of these experiments are recorded in chart 2. The curves obtained from the three normal monkeys and from monkeys M1, M2 and M3 during the control period indicate a rapid withdrawal of the dye from the blood of the normal Macacus rhesus. Only small quantities were found in the blood ten minutes after injection. A progressively increasing retention in the course of the disease is illustrated by monkeys M1, M2, M3, M6, M7 and M8. The excretion was abnormally slow in all cases of yellow fever.

Differences in the rate of progress of the disease are demonstrated by monkeys M1, M3, M7 and M8. In M1 and M3 there was only a slight abnormal retention on the second day of fever, while in M7 and M8 retention was almost complete on the corresponding day. The illness was much shorter in the latter two monkeys and terminated fatally on the fourth and third days, respectively, after inoculation. Considerable retention occurred in monkeys M7 and M8 on the day following infection, before any febrile reaction was evident. In Macacus rhesus M1 marked retention of the dye did not occur until the fifth day of fever. The animal died on the following day.

3. *Fibrin and Clotting Time of the Blood.*—The average clotting time of normal monkey blood (fourteen cases) determined by Lee and White's method,[4] at room temperature (from 80 to 95 F.), was slightly less than two and one-half minutes, with a minimum of one and one-half minutes and a maximum of four minutes. In eleven of the cases studied, the coagulation time during yellow fever was greater than the

6. Wakeman and Morrell.[1a, b, c]

normal average, the greatest increases being on the second day of the fever or later. In one case the clotting time decreased as the fever progressed, while no change was observed in the remaining two cases.

Determinations of blood fibrin were made on eight monkeys. From these, only three values were obtained, from presumably normal animals. Expressed as milligrams of fibrin nitrogen per hundred cubic centimeters

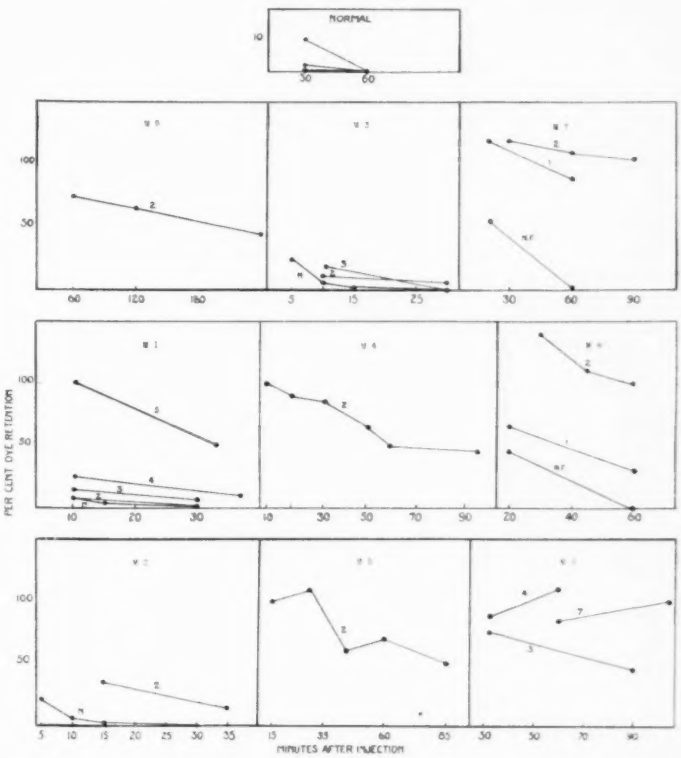

Chart 2.—Bromsulphalein tests in yellow fever. The numbers beside the curves indicate the day of fever on which the test was performed. *NF* signifies that the monkey was infected but had not yet shown fever. *N* signifies that the monkey had not yet been infected.

of plasma, these were 35, 72 and 138. Values determined on the first day of fever were in every case larger than these, ranging from 199 to 213 mg. The fibrin nitrogen in the blood of two monkeys that died on the fourth and fifth days of fever was 14 and 39 mg., respectively. Three other animals died on the first and second days of fever with from 128 to 213 mg. of fibrin nitrogen in the blood.

The fragility of red blood cells in monkeys with yellow fever did not differ significantly from that in the normal monkey.

COMMENT

A considerable increase in the quantity of bilirubin in the blood occurred in most of the monkeys during yellow fever (chart 1). Values obtained from normal serum, which were recorded as zero or faint traces, have been included in the first column of the chart. Only one animal died with less than 0.2 mg. of bilirubin per hundred cubic centimeters of blood. Large variations were found in the amount of pigment in the blood just before death. The figures range from 0.2 to more than 8 mg., while occasionally 2 mg. or more was found several days ante mortem. No correlation was found between the length of the febrile period and the amount of bile pigment. One monkey with a fever protracted as long as six days died with less than 3 mg. of bilirubin in the blood, while another had more than 9 mg. on the second day of fever (chart 1). Excretion of bile pigment is similar to other functions of the liver in this respect,[6] as the degree of functional loss does not depend on the duration of the illness. However, the accumulation of bile pigments in the blood was noted in most cases before other abnormalities became evident. In five cases in which daily observations were made, increases in the bilirubin content of the blood were noted from one to four days before death.

Only one monkey which passed safely through the disease was studied. Three observations were made, one on the first and one on the fourth day of fever, and one on the seventeenth day after inoculation, when the animal had recovered. No increase in bile pigment was noted except for a faint trace which occurred on the fourth day of fever. It is possible that any appreciable accumulation of bilirubin in the blood indicates a fatal prognosis. Klotz and Simpson [7] have pointed out that patients may die of yellow fever with little or no jaundice occurring. The one monkey that died with less than 0.2 mg. of bilirubin, as well as two others that showed less than 1 mg. of bilirubin, may be classed with cases of this type. Estimations of amino-acid nitrogen, nonprotein nitrogen and sugar in the blood of these monkeys indicated a loss of hepatic function considerably greater than one would infer from the accumulation of bile pigments. Klotz and Simpson ascribed this phenomenon to an inhibited formation of bile pigment due to damage to the reticulo-endothelial system.

Considerable variability was shown in the different types of the van den Bergh reaction observed. The reactions ranged from the

7. Klotz, O., and Simpson, W.: Jaundice and Liver Lesions in West African Yellow Fever, Am. J. Trop. Med. **7**:271 (Sept.) 1927.

indirect, through the biphasic, to the immediate direct type. In general the indirect van den Bergh reaction was obtained early in the course of the disease when the bilirubin content of the blood was low, and became immediate and direct as the bilirubin increased.

The results of the bromsulphalein liver function tests (chart 2) give further evidence of loss of hepatic function in the disease. An abnormally high retention of the dye is among the earliest manifestations of the hepatic lesions produced by yellow fever. In monkeys M7 and M8 such retention occurred while the temperature and blood sugar were in the normal range. In the cases of these two animals the abnormality in the excretion of dye was accompanied by a difficulty in disposing of injected dextrose, although the fasting blood sugar remained normal until the last day of life.[1d] In monkeys M1, M3 and M5 tests were made more than twenty-four hours ante mortem, and marked losses in their ability to excrete the dye appeared a considerable time before any other evidence of progress of the disease was apparent. That changes occur in the ability of the liver to remove the dye from the blood many days before death is shown in the data for monkeys M1, M3, M6, M7 and M8 (chart 2). Macacus rhesus M6 showed a high retention as early as four and a half days before death. The first curve from this animal was obtained on the third day of fever, four days after inoculation. Although the dye retention was abnormally high, the nonprotein nitrogen, urea, amino-acid and blood sugar were normal. The blood sugar remained normal until three days later, when it dropped to 41 mg. per hundred cubic centimeters twenty-six hours ante mortem. The urea and amino-acid nitrogen were unchanged until the last day of life. In this monkey an impaired excretion of dye was demonstrated before other changes took place. Similarly, in monkeys M1, M2, M3, M7 and M8 the blood sugar remained normal after the rate of excretion of bromsulphalein had decreased. The blood sugar was the first of the substances previously reported to respond to changes in hepatic function during yellow fever. An alteration in the blood sugar was noted as early as fifty hours before death,[1e] but in every case presented in chart 2 this was preceded by an abnormal retention of dye.

An increased coagulation time of the blood during yellow fever has been noted in cases in human beings. Some evidence has been presented here that the blood of Macacus rhesus monkeys also clots more slowly during the disease. The results of the determinations of blood fibrin suggest that the increased clotting time may be the result of a decrease in blood fibrinogen. The effect of blood calcium has been ruled out, since no significant changes were found in the calcium content of the blood during yellow fever.[1e] The fibrinogen content of the blood was found to increase during the first days of fever; but when fever was prolonged until the third and fourth days or beyond, the animals died

with a low blood fibrinogen. McMaster and Drury [8] and Foster and Whipple [9] have ascribed to the liver the origin of blood fibrinogen. Destructive lesions produced by yellow fever may, in the early stages of the disease, stimulate the formation of fibrinogen, while in the longer febrile periods the effect of the hepatic lesions may become apparent through decreased blood fibrinogen.

Himwich, Goldfarb and Weller [10] have recently demonstrated that the liver is the chief site of acetone production. These investigators, working with depancreatized dogs, based their conclusions on the acetone content of blood entering and leaving such organs as the liver, muscle, kidney and the viscera drained by the portal vein. In the present studies of experimental yellow fever a number of qualitative tests for acetone in the urine were made by means of the sodium nitroprusside reaction. The specimens of urine tested were from monkeys that had shown a low blood sugar for a considerable period before death. No positive test for acetone was obtained from the urine of these monkeys. On the other hand, the urine of Macacus rhesus M14, which was starved for twenty-eight days, showed from 2+ to 4+ acetone from the eleventh to the twenty-sixth day of starvation. These were the only days on which the test was performed. It is significant that monkeys dying of yellow fever and in a condition of carbohydrate starvation, with the blood sugar as low as 25 mg. for some time, excreted no acetone in the urine. All the evidence from this series of studies indicates that the liver is without normal function in the terminal stages of yellow fever. Hence, if the liver is the chief site of acetone production, little or no acetone should be present in the urine of moribund monkeys. This was found to be the case.

SUMMARY

1. The rate of excretion of bromsulphalein dye by the liver is greatly diminished in yellow fever. An abnormally great retention of the dye by infected monkeys is observed in many cases several days before death.

2. The onset of jaundice during yellow fever is manifested by an increase in the bilirubin content of the blood. The increased retention of bile pigment in the blood may begin several days before death.

3. Increasing amounts of bile pigment in the blood and, more especially, abnormally slow removal of bromsulphalein dye from the blood

8. McMaster, P. D., and Drury, D. R.: The Source of Fibrinogen, Proc. Soc. Exper. Biol. & Med. **26**:490 (March) 1929.

9. Foster, D. P., and Whipple, G. H.: Fibrin Values Influenced by Cell Injury, Inflammation, Intoxication, Liver Injury, and the Eck Fistula: Notes Concerning the Origin of Fibrinogen in Body, Am. J. Physiol. **58**:407 (Jan.) 1922.

10. Himwich, H. E.; Goldfarb, W., and Weller, A.: Effect of Various Organs on Acetone Content of Blood in Phlorhizin and Pancreatin Diabetes, J. Biol. Chem. **93**:337 (Oct.) 1931.

are the first indications of loss of hepatic function in monkeys suffering from yellow fever.

4. Some evidence is presented showing that the clotting time of blood is usually prolonged in yellow fever.

5. The increased clotting time is associated with a lowered fibrinogen content of the blood.

6. Monkeys dying of yellow fever do not excrete acetone in the urine. This fact supports the evidence that the liver is the chief site of acetone formation.

THROMBO-ANGIITIS OBLITERANS AMONG WOMEN

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Thrombo-angiitis obliterans usually affects men between the ages of 20 and 45 years. Although approximately seven hundred cases of thrombo-angiitis obliterans have been observed at the Mayo Clinic, the present report of ten cases is the first series among women to be put on record. The diagnosis in three of these cases was proved by a study of the pathologic changes in the occluded arteries and veins. Only three acceptable cases have been reported in the literature (cases 1, 2 and 3). In 1924, Buerger [1] made a clinical diagnosis of the condition of two women without proof of pathologic changes. In 1925, Meleney and Miller [2] reported that they had observed a Chinese woman with thrombo-angiitis obliterans; their study of the occluded vessels leaves no doubt as to the diagnosis. Koyano [3] reported the case of a woman, aged 55, in whom a peculiar vascular disturbance had appeared in the left leg following influenza, necessitating amputation. Data are inadequate to substantiate the diagnosis of thrombo-angiitis obliterans. Telford and Stopford [4] reported two cases of occlusive vascular disease in women, but in our opinion these did not represent cases of thrombo-angiitis obliterans. Trabaud and Chaty [5] reported a case of obscure vascular disturbance in the extremities of a Mohammedan girl, aged 20, which does not conform to that observed in cases of thrombo-angiitis obliterans.

From the Division of Medicine, the Mayo Clinic.

1. Buerger, Leo: The Circulatory Disturbances of the Extremities, Including Gangrene, Vasomotor, and Trophic Disorders, Philadelphia, W. B. Saunders Company, 1924.

2. Meleney, F. L., and Miller, G. G.: A Contribution to the Study of Thrombo-Angiitis Obliterans, Ann. Surg. **81**:976 (May) 1925.

3. Koyano, K.: A Clinical Study of One Hundred Cases of Thrombo-Angiitis Obliterans Among the Japanese, Acta scholae med. univ. imp., Kioto **4**:489 (April) 1922.

4. Telford, E. D., and Stopford, J. S. B.: Two Cases of Thrombo-Angiitis Obliterans in Women, Brit. M. J. **1**:1140 (June 25) 1927.

5. Trabaud, J., and Chaty, Choukat: Étude microscopique des lésions dans un cas de maladie de Léo Buerger chez une femme musulmane, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:583 (April 6) 1931. Trabaud, J., and Mredden: Maladie de Léo Buerger chez une jeune fille musulmane, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:579 (April 6) 1931.

ABSTRACTS OF CASES REPORTED IN THE LITERATURE

CASE 1 (Buerger).—A Jewess (age not stated) was observed in February, 1912. She gave an indefinite history of right "sciatica" followed from three to four months later by pain in the right foot, coldness, pallor and intermittent claudication.

General examination was negative except for the condition of the right lower extremity. Pulsations could not be felt in the right posterior tibial artery. All of the other peripheral arteries pulsated normally. Moderate rubor of the right foot in the dependent position and moderate ischemia, when the foot was elevated, were noted. The patient was again observed in June, 1912. Shortly after her first examination she received a burn on the right foot, and an ulcer developed under the nail of the right great toe. The nail came off, and the nail bed healed in four weeks. A few weeks later, the right foot became badly affected, the toes looked almost black, and amputation of the foot was advised. The nail bed of the right great toe was gangrenous. Amputation was refused; the symptoms in the foot gradually subsided, and healing took place. Pulsations were absent in the right dorsalis pedis and the right posterior tibial arteries. Rubor and blanching of the foot were more marked than at the time of the first examination. The patient was again observed in January, 1913. Both feet were slightly cold. Evidence of atrophy was not present. The right foot showed definite rubor in the dependent position. On elevation, both feet were distinctly blanched. Pulsations could not be felt in the right dorsalis pedis, right posterior tibial and left dorsalis pedis arteries. In June, 1912, the right foot had become distinctly warmer, and the patient considered herself much improved. Examination disclosed the same condition of pulsations as at the previous examination.

The clinical course in this case, with the history of intermittent claudication and evidence of slowly progressing occlusive vascular disease in the right foot, followed later by a similar occlusive vascular process in the left foot, leaves little doubt as to the correct clinical diagnosis of thrombo-angiitis obliterans.

CASE 2 (Buerger).—A woman, aged 38 (nationality not stated), began to have pain in the calf of the right leg on walking following an attack of influenza two years previously. The right leg became swollen, but after six months the cramps in the calf disappeared; the swelling, however, persisted, and all the toes were numb. Eight months before examination the right foot had become cold, and the patient had noticed a red spot on the inner aspect of the right leg.

General examination revealed edema of the right foot and leg, more marked over the ankle. The great toe was hemorrhagic, showing evidence of discoloration of the tip with ecchymosis. There was moderate erythromelia over the forepart of the right foot. Elevation elicited considerable ischemia. On a return to the horizontal position, the color did not appear for some time; rubor appeared first above the roots of the toes, and the toes themselves remained ischemic and cyanotic. Pulsations in the dorsalis pedis and posterior tibial arteries of the right foot were absent; those of the left foot were present.

We are inclined to accept this as a true case of thrombo-angiitis obliterans, and think that the clinical course justifies this diagnosis. It is possible, however, that this case represents the same type of condition as represented by the case reported by Koyano.

CASE 3 (Meleney and Miller).—In October, 1921, a woman, aged 48, complained of having had severe pain in the right foot for five or six years and ulceration of the distal end of the foot for three years. Five years before examination the great toe had received some sort of trauma. Following this the nail sloughed off; the wound took five months to heal, and the general pain in the foot continued. Two years later all of the toes became black and slowly separated. The bases never healed over. Pain steadily increased. The history was irrelevant except for the fact that the feet had been bound in childhood.

The right foot was small and covered with tight skin. All of the toes were missing, and there was a granulating ulcer in the region of the bases of the toes with a protrusion of the heads of the first and second metatarsal bones. Around the ulcer, the skin had the purplish color of gradually dying tissue. There was no sharp line of demarcation. The dorsalis pedis artery could not be felt. The popliteal artery was palpable, but there was less volume than on the other side. The urine was normal. The Wassermann reaction of the blood was negative. Roentgenograms disclosed decalcification of the bones but no osteomyelitis. The arteries were not visible.

The leg was amputated at the middle. The edges of the wound became gangrenous, and the tissue above became dusky. The wound opened. Staphylococcus aureus was recovered in cultures from the fluid. The wound gradually healed in three months. An old obliterating thrombus was found in both the anterior and the posterior tibial arteries with secondary canalization. The dorsalis pedis had not only the old process, but also evidence of a relatively more acute process, as shown by the presence of giant cells.

The clinical course in this case, the closure of the right dorsalis pedis and right posterior tibial arteries, with auto-amputation of all the toes, and the pathologic changes in the arteries and veins in the amputated extremity make the diagnosis of thrombo-angiitis obliterans certain.

CASE 4 (Koyano).—A housewife, aged 55, had experienced languor soon after an attack of chills and high fever with fits of coughing in January, 1920 (during an epidemic of influenza). Twelve days afterward she had noticed a dark red spot on the middle of the left leg and cyanosis of the foot; the pain kept her from moving. The spot spread toward the terminus and turned dark brown.

The left leg was amputated at the middle. Histologic examination of one of the internal saphenous veins disclosed an obliterating clot in the early state of the organizing process. In the center of the clot was a so-called purulent focus, similar to that of thrombo-angiitis obliterans.

The clinical course in this case does not suggest thrombo-angiitis obliterans. The fact that it followed influenza suggests that the lesion in the left leg was acute arteritis rather than the more chronic occlusive arterial lesion such as usually obtains in thrombo-angiitis obliterans. The histologic proof of the internal saphenous vein is not convincing. Koyano did not mention the type of lesion that was found in the arteries of the amputated extremity. Notes were not made regarding pulsation in the extremity that was subsequently amputated or in the other extremities.

CASE 5 (Telford and Stopford).—A woman, aged 52, born in England, had had severe aching pain in the index and middle fingers of the left hand for fifteen months. The fingers became slightly blue. Within three weeks the whole hand ached severely, and was cold and dark red. Within three months after the onset of symptoms, dry gangrene of the left hand and the lower part of the forearm developed. The pain then ceased, and no change in the extremity was observed during the following twelve months. For the greater part of her life the patient had worked in a dye works with her hands continually in cold, running water.

The heart was normal. The pulse in the head, neck and right arm was normal. Pulsations were absent in the vessels of the left arm. In both lower extremities a slight pulse could be felt in the popliteal artery but at no other point below this. Sensation in the left arm, above the gangrenous area, was normal. The patient died shortly afterward from "malignant ovarian cyst." Specimens of the blood vessels were not obtained for examination.

This is an unusual type of case, but can hardly be called thrombo-angiitis obliterans. The presence of a malignant ovarian cyst may well explain many of the vascular phenomena observed.

CASE 6 (Telford and Stopford).—A woman, aged 48, born in England, had first noticed weakness of the left hand six years previously. The weakness progressed, and there were tingling and aching of the forefinger. Within a year, the right arm followed the same course, but the trouble was never so severe.

Both arms were weak and much wasted. There was no alteration of sensation, sign of a nerve lesion, discoloration or other gross evidence of circulatory trouble. Pulsations in the head and neck were normal, but were entirely absent in the upper extremities. The patient stated that her legs tired easily and often "went to sleep." In the right lower extremity a feeble pulse could be felt in all the large vessels, but in the left lower extremity pulsation could not be felt in or below the popliteal artery. The femoral pulse on the right side was very faint. Sixteen years prior to the onset of the patient's present symptoms, pulsations could not be detected in the upper extremities.

We are unable to classify this case. The onset of weakness in the left hand, followed later by marked wasting of both arms, certainly does not suggest the clinical picture observed in thrombo-angiitis obliterans.

CASE 7 (Trabaud and Chaty).—A Mohammedan girl, aged 20, entered the hospital because of trophic disturbances of the hands and feet which had been present for four years. Burning and pain in the extremities, nocturnal attacks of pain and attacks of what had been termed hepatic colic associated with jaundice were present. For a period of about a month she had had cyanosis of the fifth finger of the right hand, and this process extended to the fourth finger and then to the third. The same condition appeared in the third finger of the left hand and the fifth toe of the right foot.

Examination disclosed dry gangrene of the third, fourth and fifth fingers of the right hand, and cyanosis of the right index finger and thumb. There was also dry gangrene of the first, third and fifth fingers of the left hand as far as the first joints, and cyanosis of the fourth finger and thumb. Gangrene of the first, second, third and fourth toes of the right foot was present, and cyanosis of the first toe of the left foot, with several bluish plaques on the second toe of the left foot. The disease progressed rapidly. The feet, legs and forearms became cyanotic,

and gangrene appeared on the tip of the nose and on the lobe of the right ear, and deep sloughs appeared over the sacrum, heels, trochanters and elbows. The nose sloughed off. The patient died thirty-eight days after admission to the hospital, and was in coma a short period before her death. She had drunk two thirds of a liter of wine daily for years.

A partial postmortem examination was carried out. The radial, brachial and femoral arteries were not occluded, and the caliber was not reduced. The intima appeared normal. The small arterioles in the extremities were almost completely obliterated by endarteritis. This obliterative process was due to thickening of the intima. Marked intimal proliferation was also noted in the small vessels of the kidneys and ovaries. A diagnosis of Buerger's disease was made. Accurate observations were not made on the pulsations of the peripheral arteries.

It is impossible to determine the nature of the disease in this case, but it certainly was not Buerger's disease.

CASES OBSERVED AT THE MAYO CLINIC

CASE 8.—A woman, aged 44, of Norwegian parentage, came to the clinic on April 8, 1925, because of pain in the left foot of two years' duration. She had first observed sharp pain in the sole of the foot, which was present when at rest, but at times was worse with exercise. This intermittent type of pain seemed to become localized in the third and fourth toes; they became cyanotic; an ulcer developed on the fourth toe, and it was amputated on May 29, 1924. Two months later the patient resumed her usual duties and felt well. There was no history of superficial phlebitis. Three weeks prior to admission to the clinic, the third left toe and base of the first toe ulcerated and caused pain sufficient to disturb her sleep. Pain when at rest was present at the time of admission. She had been married twenty-five years and had three children who were living and well; she had had three self-induced abortions. Her health had been good. She had used tea and coffee to excess and had used alcohol moderately.

The patient was 63 inches (160 cm.) in height and weighed 109 pounds (49.4 Kg.). General examination was negative except for the condition of the extremities. Small ulcers (fig. 1) were present on the tip of the third toe and at the base of the first toe of the left foot. The fourth toe had been amputated. Arterial pulsations were normal in the right lower extremity, and in the left femoral and left popliteal arteries, but pulsations could not be felt in the left foot. Pulsations in the left leg and foot could not be elicited with the oscillometer. When the feet were elevated, there were pallor, graded 1, of the right toes, and pallor, graded 3, of the left toes. With the feet hanging in the dependent position, rubor graded 2 was observed in the first and third left toes in one and a half minutes. Definite rubor was not observed in the right foot. Observations were not made regarding pulsations in the arteries of the upper extremities. Roentgenograms of the feet and legs were negative for the presence of calcified vessels. The blood pressure, in millimeters of mercury, was 130 systolic and 75 diastolic. Repeated examinations of the urine gave negative results. The concentration of hemoglobin (Dare) was 70 per cent, and the acid hematin was 13.3 Gm. for each 100 cc. of blood. The erythrocytes numbered 4,230,000, and the leukocytes 6,900 in each cubic millimeter of blood. The concentration of urea was 34 mg.; creatinine, 1.3 mg., and uric acid, 3.5 mg. in each 100 cc. of blood. The whole blood fibrin was 278 mg., and the plasma fibrin, 420 mg. in each 100 cc. of blood. The return of phenolsulphonphthalein in the urine was 60 per cent in two hours. The Wassermann reaction of the blood was negative.

On April 20, 1925, the left foot eliminated 0.44 calories per minute per square inch of skin surface. One week later, the left foot eliminated 0.72 calories per square inch of skin surface, which indicated a definite increase in the flow of blood to the foot, following rest in bed with radiant heat applied from eight to twelve hours a day, postural exercises and contrast baths. Marked relief from pain followed the intravenous use of radium chloride on two occasions. The first injection was 10 micrograms and the second 25 micrograms. The patient was under observation for twenty days, and was free from pain when dismissed from the clinic.

A letter from the patient received on May 7, 1927, stated that the amputation of a toe had been necessary in 1926; the left foot felt cold, and she was having considerable pain. A letter written in April, 1928, stated that she was having the

Fig. 1 (case 8).—The appearance of the left foot. Ulcers are present at the base of the first toe and tip of the third toe; the fifth toe had been amputated.

same symptoms in the right foot, and that the right toes were sore. A letter written in September, 1928, stated that the patient had been in bed for six weeks with pain in both feet and gangrene in one toe. It has been impossible to obtain additional follow-up information in this case.

This case represents the first one of thrombo-angiitis obliterans observed in a woman at the Mayo Clinic. Unfortunately, the data are not adequate to establish a definite diagnosis. There is no doubt of the fact that the patient had occlusive vascular disease of the lower extremities with severe pain, trophic changes and gangrene, which necessitated the amputation of two toes. In the absence of demonstrable sclerosis in the peripheral arteries and the clinical course of the disease, it seems highly probable that the occlusive vascular process

was of the nature of thrombo-angiitis obliterans rather than of arteriosclerosis. If the same clinical picture had been observed in a man of the same age, we should not have hesitated to make a diagnosis of thrombo-angiitis obliterans.

CASE 9.—A woman, aged 43, first came to the clinic in January, 1929, complaining of numbness and blueness of the fingers of four years' duration. A diagnosis of Raynaud's disease had been made elsewhere. She had had scarlet fever at the age of 5 years, diphtheria and smallpox at 15 and erysipelas at 21. Subtotal thyroidectomy had been performed at the age of 25, tonsillectomy at 32 and appendectomy and uterine suspension at 33. She had been married thirteen years and had had one stillborn infant. Four years prior to admission she first observed numbness in the right fourth finger when sewing and using a thimble. A few months later, pallor of all the fingers to the second joint, followed by cyanosis and numbness, was observed. For the last two winters the same color reaction (pallor and cyanosis) was also observed in the toes and ears. This had become progressively worse, and at the time of admission, there were mild cyanosis and tingling sensations in the tips of the fingers.

The patient appeared healthy. She was 62 inches (157.5 cm.) in height, and weighed 167 pounds (75.7 Kg.). General examination was negative except for mild obesity and small varicose veins along the left leg. All of the usual palpable arteries in the upper and lower extremities pulsated normally. Scleroderma was not present. The blood pressure was 124 systolic and 76 diastolic. Repeated examinations of the urine gave negative results. The concentration of hemoglobin (Dare) was 78 per cent, and the acid hematin was 17.5 Gm. for each 100 cc. of blood. The erythrocytes numbered 4,710,000, and the leukocytes, 10,100. The differential count showed 25 per cent lymphocytes, 1 per cent transitionals and 74 per cent neutrophils. The blood platelets numbered 220,400 and the bleeding time (Lee) was three minutes. Viscosity of the blood was 5.3 (normal 4.5). The Wassermann reaction of the blood was negative. Examination of the ocular fundi and roentgenograms of the teeth gave negative results. When the patient was under observation, superficial migrating thrombophlebitis along the lower part of the right leg developed. A segment of the acutely thrombosed vessel was removed and cultured. Negative results were obtained. The microscopic appearance of the vessel obtained at biopsy was essentially the same as that previously observed in similar vessels from known cases of thrombo-angiitis obliterans in men.

The patient came to the clinic with the idea of having a bilateral dorsal sympathetic ganglionectomy performed, but the mild symptoms did not seem to justify the operation. She returned in September, 1930, for a short period of observation. There had been no progression of symptoms. She received deep roentgen treatment over the upper part of the cervical spine on September 24, October 22 and November 19, but striking effects were not obtained. General examination on Dec. 17, 1930, disclosed closure of the right ulnar artery and the right and left posterior tibial arteries. The other palpable arteries pulsated normally. Postural color changes were not observed. A telegram from this patient dated March 12, 1931, stated that superficial phlebitis of the left leg, just below the knee, had developed. It appeared to be of the same type as that previously observed on the right leg.

The patient was again admitted to the clinic on April 21, 1932, because of superficial phlebitis of the left leg, which had failed to respond to medical treatment at home. Two large areas of superficial phlebitis, involving the upper third of the left leg, were present. Under local anesthesia, these areas were completely resected

the day after admission to the clinic. Cultures of small segments of the vein gave negative results. The microscopic appearance of the vessels revealed a chronic inflammatory process involving the entire walls of the veins, with round cell infiltration around the vasa vasorum and giant cells in the occluded lumens. Pulsations in the peripheral arteries were the same as on the previous admission.

CASE 10.—A Jewess, aged 60, registered at the clinic on Feb. 25, 1929, and was under observation until April 10. She was again admitted on May 16, and remained until the time of her death, June 28. Prior to her admission she was under observation in an excellent hospital elsewhere for four weeks, where a diagnosis of occlusive vascular disease of the right leg was made. At the time of her first admission to the clinic the disease of the right leg had been present for approximately five or six weeks. She did not speak English, and a history of the case was obtained through an interpreter. Approximately five or six weeks prior to her first admission she was confined to bed for a period of three days with tonsillitis. When lying in bed convalescing from this condition, she was suddenly seized with a sharp pain in the right foot. The toes became white, numb and painful. Later they became cyanotic. The pain was most marked in the sole of the foot. This pain was still present when she was admitted to the clinic. In the last two years she had had small subcutaneous nodules on both legs, which seemed to appear for a few days and reappear later in an adjacent area. It could not be determined whether these represented areas of superficial phlebitis, but probably they did, in view of the fact that acute superficial phlebitis developed along the inner aspect of the right leg and thigh three days after admission. There was no history of intermittent claudication. She had never used tobacco in any form.

General examination was essentially negative except for the condition of the extremities. All of the palpable arteries in the upper extremities pulsated normally, as did both femoral arteries. Definite pulsations could not be felt in the right popliteal, right dorsalis pedis and right posterior tibial arteries. Good pulsations could be felt in the same arteries in the left leg. Ulcers were not present. The right leg was swollen and edematous, graded 1 to 2. The circulation seemed normal in the left leg. When the right leg was elevated, there was blanching, graded 1, and rubor, graded 1 to 2, with the foot in the dependent position. The foot felt cold. Readings of blood pressure taken daily showed a range of from 100 to 136 systolic and from 50 to 80 diastolic. The average readings were 120 systolic and 76 diastolic. Repeated examinations of the urine gave negative results. The concentration of hemoglobin (Dare) was 75 per cent; the erythrocytes numbered 4,600,000, and the leukocytes, 11,500. The differential count was normal. The acid hematin was 12.9 Gm. for each 100 cc. of blood. The urea was 14 mg. and the sugar 89 mg. in each 100 cc. of blood. The Wassermann reaction of the blood was negative. Roentgenograms of the right foot and leg were negative for calcified vessels, but showed slight atrophy of bone with slight hypertrophic changes of the tarsal bones, and spurs on the calcaneum. Roentgenograms of the pelvis were negative. The ocular fundi were reported normal.

Three days after admission migrating thrombophlebitis developed which in a period of four weeks extended along the great saphenous vein from below the right knee to the groin. Approximately forty-eight hours after the phlebitis first appeared, a specimen was obtained for biopsy from the acutely thrombosed vein. Numerous cultures of the resected vein did not reveal a growth of organisms. The microscopic appearance of the vein was the same as that which we have seen from numerous veins obtained in a similar manner from known cases of thromboangiitis obliterans in men (fig. 2). The edema of the foot and leg, which was present on admission, disappeared in three or four days but reappeared about four

weeks later, with symptoms that indicated deep thrombophlebitis of the right thigh. By April 10, clinical evidence of thrombophlebitis had disappeared. The foot felt warm; the cutaneous temperature was 30 C. When the patient was dismissed from observation she was free from pain, and remained so until three or four days prior to her second admission, on May 16. She then had severe pain in the right foot. The right femoral artery still pulsated normally but pulsations could not be felt in the remainder of the extremity. Pulsations in the left lower extremity were normal. When the right foot was elevated there was blanching,

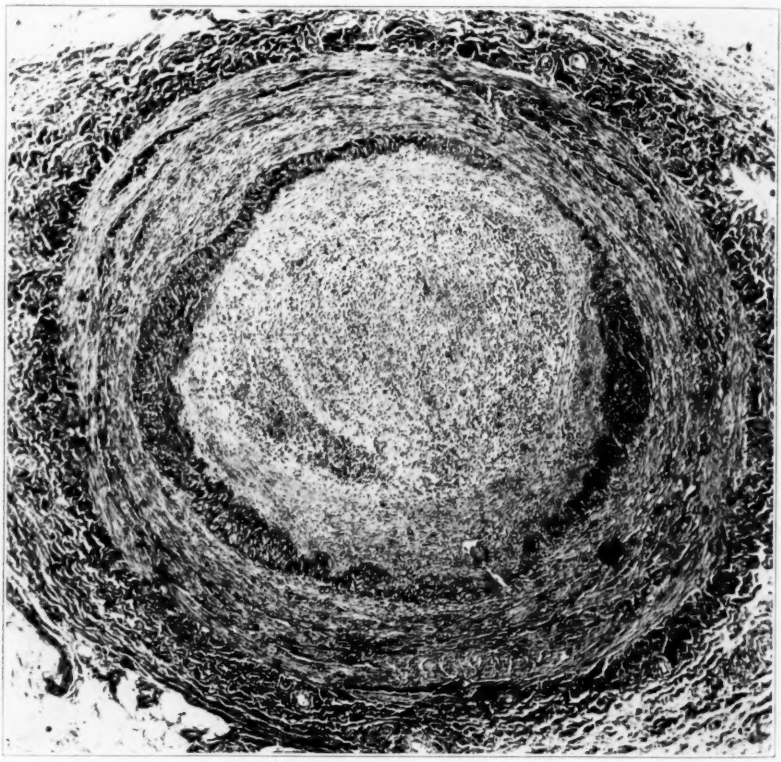

Fig. 2.—Cross-section of a small superficial vein obtained at biopsy. The lumen is occluded with a cellular thrombus, and a chronic inflammatory reaction involves the wall of the vessel. Hematoxylin and eosin stain; × 40.

graded 3, with rubor and cyanosis, graded 3 to 4, with the foot in the dependent position. Edema was not present, and the results of the remainder of the general examination were the same as on the first examination.

The use of typhoid vaccine and the usual medical measures failed to relieve the pain, and on May 23 it was necessary to amputate the right leg at the juncture of the lower and middle third of the thigh. The condition did not improve following the operation. There was gradual thrombosis of the right femoral artery, and the stump failed to heal. The patient gradually failed, and died with terminal

bronchopneumonia on June 28. Necropsy was not obtained, but the microscopic appearance of the vessels from the right leg showed the picture characteristic of thrombo-angiitis obliterans (figs. 3, 4 and 5).

Case 11.—A Jewess, aged 21, first registered at the clinic on May 24, 1929, complaining of a "drawing numbness" in both feet, which came on only after exercise, and which had been present since January 1. She also complained of "twitching pain" in the feet which came only at night when she was in bed; this began about March 1. She had considered herself in good health until the onset of her present illness. She was married and had one child, aged 19 months. There was no history of a miscarriage. Her husband was living and in good health. When walking on January 1, the patient first experienced a tired feeling in the calf muscles of both legs, which, however, was not sufficient to cause her to stop walking. Since that time she had always had a drawing sensation or pain in the calves of both legs after walking four or five blocks. Complete relief had been obtained either from standing or from sitting for a minute or two, with

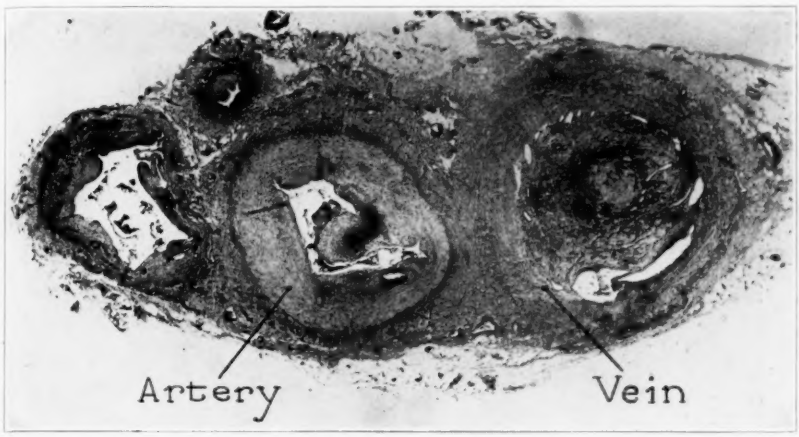

Fig. 3.—Cross-section of the posterior tibial artery and vein. The larger vein is occluded by a chronic thrombus, and the artery is partially occluded by an organized thrombus. The artery and vein are closely bound together by a chronic inflammatory process. Hematoxylin and eosin stain; × 15.

recurrence of the pain after she again walked a stated distance. She had never had this pain except after walking and it had been symmetrical. At the time of admission, she could walk only one block without pain in the legs. About March 1, she began taking capsules for this pain (intermittent claudication), and following this, at night, she frequently had twitching and a numb sensation in the toes of both feet, especially of the right foot. Occasionally she experienced a sensation of heat in the toes. She had discontinued taking the capsules three weeks prior to admission to the clinic.

General examination revealed a well developed and well nourished woman whose height was 64 inches (162.6 cm.) and weight 120 pounds (54.4 Kg.). Neurologic examination gave negative results. The blood pressure in the upper extremities ranged from 110 to 136 systolic and from 70 to 80 diastolic. We were unable to obtain blood pressure readings in the lower extremities. The pulsations in the

right brachial artery were almost normal, graded 3, and those in the left were normal. The pulsations of the right and left radial arteries and of the right and left ulnar arteries were almost normal. The abdominal aorta pulsated normally. Pulsations of the right femoral artery were normal, but were slight of the right

Fig. 4.—Cross-section of the posterior tibial vein, which is a high power view of the vein in figure 3. The chronic nature of the occlusive process and the attempt at canalization may be observed. Hematoxylin and eosin stain; × 50.

popliteal, right posterior tibial and right dorsalis pedis arteries. Pulsations of the left femoral artery were approximately normal; those of the left popliteal, fairly normal, and those of the left posterior tibial and left dorsalis pedis, slight (fig. 6*a*). With the feet elevated, there was marked blanching at 180 F., the feet assuming

a cadaveric appearance, and with the feet in the dependent position, there was rubor, graded 1, of the toes.

Examinations of the urine were negative except for the presence of small amounts of lead. One specimen of 600 cc. of urine contained 0.14 mg. of lead; a second specimen of 500 cc. contained 0.21 mg., and a third specimen of 600 cc. contained 0.07 mg. Arsenic was not found in the urine. The concentration of hemoglobin (Dare) was from 70 to 75 per cent; the erythrocytes numbered 4,800,000, and the leukocytes, 9,400. The differential count showed the following percentages: lymphocytes, 31; large mononuclears, 1; transitionals, 1, and neutrophils, 67. The platelets numbered 224,000, and the bleeding time was three and a

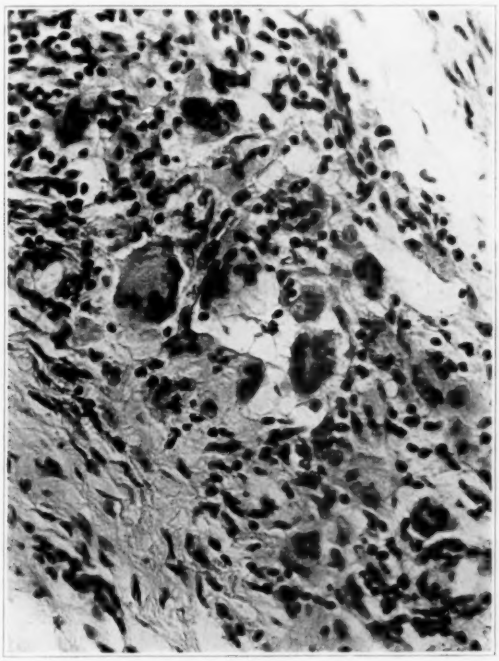

Fig. 5.—A high power view of figure 2; giant cell formation may be noted. Hematoxylin and eosin stain; × 300.

half minutes. The coagulation time (Lee) was ten and a half minutes. The acid hematin was 13.9 Gm. for each 100 cc. of blood. There was no basophilic stippling of the erythrocytes, and no lead line around the gums. The Wassermann reaction of the blood was negative. Roentgenograms of the thorax and teeth were negative. The tonsils had been removed elsewhere when the patient was 8 years of age. Foci of infection were not found. Examination of the ocular fundi was negative, except for compound myopic astigmatism. The vasomotor index of the right and left foot was 0, whereas that of the left hand was 4.

Treatment was instituted with radiant heat, postural exercises, contrast baths and intravenous injections of typhoid vaccine. Four injections were given, the

dosage ranging from 50,000,000 to 100,000,000 organisms, with good systemic reactions (the temperature by mouth ranging from 102 to 103 F.) following each injection. The pain at night of which the patient complained at the time of admission entirely disappeared following the first injection of typhoid vaccine. Her ability to walk improved approximately 25 per cent during her twenty-two day stay in the hospital. A tentative diagnosis of thrombo-angiitis obliterans was made at the time of dismissal.

The patient continued the treatment under the direction of her home physician until the time of her second admission to the clinic on Dec. 31, 1929. During this interval she had an intravenous injection of typhoid vaccine (100,000,000 organisms) every ten days with good reactions each time. She could walk only one block at a moderate gait when claudication pain developed in both legs. She had

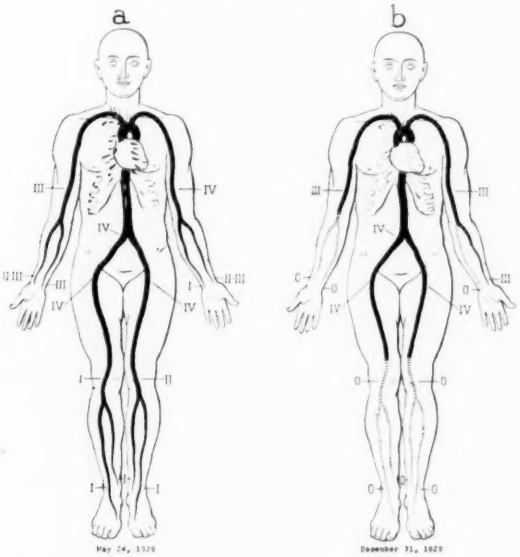

Fig. 6.—In *a*, are shown the pulsations in the arteries at the time of the patient's examination on May 24, 1929; in *b*, the pulsations in the arteries at the time of the second examination here on December 31. *o* indicates the absence of pulsations, and *IV*, normal pulsations.

never used tobacco, and there was no history of superficial phlebitis. General examination was again essentially negative except for the condition of the extremities. The blood pressure in the upper extremities varied from 105 to 108 systolic and from 90 to 95 diastolic. Both brachial arteries were open; pulsations were almost normal, but none could be felt in the right radial and right and left ulnar arteries. Pulsations of the left radial artery were almost normal, and in the femoral arteries they were normal, but no pulsations could be felt in the lower extremities below this level except an occasional feeble pulsation in each popliteal space (fig. 6*b*). Color changes were not noted in the hands when they were elevated and dependent, but when the feet were elevated, they were blanched, graded 3 to 4, with rubor, graded 2, of the toes in the dependent position. The

average temperature of the right hand at room temperature was 24 C. (75.2 F.); that of the left hand, 23.2 C. (73.7 F.); that of the right foot, 26 C. (78.8 F.), and that of the left foot, 25 C. (77 F.). The vasomotor index of the left foot was 1.9, of the right foot 2.9 and of the left hand 2.7. Examination of the urine was negative, and repeated examinations for lead were also negative. The concentration of hemoglobin (Dare) was 70 per cent; the erythrocytes numbered 4,840,000, and the leukocytes, 9,300. The concentration of urea was 21 mg. in each 100 cc. of blood, and the Wassermann reaction of the blood and a roentgenogram of the thorax were negative. The electrocardiogram disclosed a rate of 67, sinus arrhythmia, an inverted T wave in lead III, a diphasic P wave in lead III and notched Q-R-S complexes in lead III.

Bilateral lumbar sympathetic ganglionectomy was performed on Jan. 8, 1930, at which time the second, third and fourth lumbar sympathetic ganglions and connecting rami were resected. Exploration of the gallbladder, stomach, kidneys and pelvis gave negative results. Convalescence was uneventful, and the wound healed by primary intention. The patient was up on the tenth day, and was dismissed from the hospital on the sixteenth day after the operation. Following the operation, the skin of the lower extremities was warm and dry, and the temperature was approximately the same in both lower extremities. Color changes were not observed on exposure to cold. The patient stated that the feet felt normal. She reported on April 8 that she was back at work teaching, and that she was able to walk two blocks without any definite discomfort in the legs.

The tentative diagnosis of thrombo-angiitis obliterans which we made in June, 1929, seems to have been definitely confirmed by the later developments in this case. Pulsations were present in all of the palpable arteries in the upper and lower extremities at the time of the patient's first examination, although they were definitely reduced in many of the vessels, as previously stated, but at the time of the second examination, approximately six months later, the pulsations had disappeared entirely from the right radial and right and left ulnar arteries, and all pulsations were practically absent below the femoral arteries in the lower extremities, yet there were no objective trophic cutaneous changes. The closure of the arteries demonstrates conclusively the presence of occlusive vascular disease, and not vasospastic disturbance of the vessels, such as obtains in Raynaud's disease. The absence of trophic changes in the skin indicates that the development of collateral circulation has kept pace with the occlusive process in the arteries. We do not know the significance of lead in the urine in this case.

CASE 12.—A Russian Jewess, aged 47, came to the clinic on Aug. 19, 1929, because of pain in the arch of the left foot, which had been present for three weeks. Ten months prior to admission she first began to have intermittent claudication pain in the arch of the right foot and calf of the right leg, which was sufficient to cause her to stop walking at the end of two or three blocks. Rest for a minute or two while standing gave prompt relief; it was not necessary to sit down in order to obtain relief. The pain recurred when she had walked a similar distance, followed by prompt relief with rest. There had been slow but gradual improvement in these symptoms since the time of onset. Three weeks prior to

admission the same type of pain developed in the arch of the left foot, associated with rest pain. She was unable to walk fifty steps without pain at the time of admission. During the past two years the left hand and arm had felt numb if she used them very much. This numb feeling was present only after exercise, and was relieved by rest. For the last two winters she had observed that the fourth and fifth fingers of the left hand turned white when exposed to cold. There was no history of superficial phlebitis. She had never used tobacco. She had been married for twenty-three years and had three children who were living and well. Her menstrual periods were still regular. She had consulted a physician two months prior to admission because of pain in the feet and legs, and the blood pressure at that time was found to be higher than normal.

The patient was 59 inches (150 cm.) in height, and weighed 159 pounds (72 Kg.). General examination was entirely negative, except for the presence of compensatory cardiac hypertrophy, graded 1, and the condition of the extremities. The right brachial, radial and ulnar arteries pulsated normally. The left brachial artery pulsated normally. Pulsations in the left radial artery were moderate, and pulsations in the left ulnar artery were intermittent, ranging from normal to a complete absence. Pulsations of both femoral arteries were almost normal; those of both popliteal arteries, fairly normal, and those of the right posterior tibial artery, almost normal, but pulsations could not be felt in the right dorsalis pedis artery, in the left dorsalis pedis artery or in the left posterior tibial artery. When the feet were elevated, blanching, graded 1, of the toes of the left foot was present, and rubor, graded 1, of the toes with the foot in the dependent position. Postural color changes were not observed in the right foot. The surface temperature of the right foot, determined by means of the electric thermocouple, was 25.1 C. (77.1 F.), and that of the left foot, 24.9 C. (76.8 F.).[6] The surface temperature of the hands was 33.9 C. (93 F.). The vasomotor index of the right foot was 4.3, of the left foot 1.8 and of the right hand 1.1. Repeated examinations of the urine gave negative results. The concentration of hemoglobin (Dare) was 80 per cent; the erythrocytes numbered 5,310,000, and the leukocytes, 8,900. The Wassermann reaction of the blood was negative. The concentration of urea was 28 mg. in each 100 cc. of blood. The return of phenolsulphonphthalein in the urine was 60 per cent in two hours. Roentgenograms of the feet and hands gave negative results; those of the legs showed evidence of a minimal amount of calcification of the vessels. Roentgenograms of the thorax gave negative results except for cardiac hypertrophy, graded 1. Examination of the ocular fundi showed sclerosis, graded 2, of the retinal arteries of the so-called hypertension type. The blood pressure was 242 systolic and 136 diastolic. Blood pressure readings taken at hourly intervals over a period of twenty-four hours, with the patient moderately active during the waking hours, showed a range of from 170 to 230 systolic and from 110 to 140 diastolic. Similar readings obtained with the patient at rest, for a similar period, showed a range of from 160 to 215 systolic and from 80 to 140 diastolic. These observations indicated relatively severe benign hypertension. The electrocardiographic report did not indicate significant changes. The patient was placed on our usual hypertension regimen, with postural exercises, contrast baths and radiant heat for the lower extremities.

This patient had occlusive vascular disease involving the lower extremities and the left arm. Considering her age and the involvement of the upper extremities, it is possible that the condition was of

6. All surface temperatures were taken under controlled conditions, following rest and with the room temperature from 24 to 26 C. (75.2 to 78.8 F.).

the nature of thrombo-angiitis obliterans, with superimposed arteriosclerosis. The intermittent pulsations in the left ulnar artery are suggestive of thrombo-angiitis obliterans, as intermittent pulsations are frequently observed in this disease. Occlusion of the arteries in the upper extremities is rare in cases of simple arteriosclerosis. One cannot, of course, be sure of the true nature of the occlusive process.

CASE 13.—An unmarried woman, aged 28, of Scotch-Irish descent, came to the clinic on May 26, 1930, with a condition diagnosed as Raynaud's disease. Her history dated back over a period of sixteen years. At the age of 5 years, a condition diagnosed as tuberculous lymph nodes of the neck had developed. These were removed thirteen years later. It was not determined whether these represented tuberculous lymph nodes. At the age of 12 years, a crop of boils had appeared on both legs, and about the same time she first noticed cramplike pains in her feet and legs, which were thought to be rheumatic. In the last twelve years, she had continued to have attacks of superficial "abscesses" along both legs, at irregular intervals up to the time of her admission to the clinic. The cramplike pains, which probably were not the pains of intermittent claudication, continued, and two years prior to admission she finally resorted to the use of opium for relief from pain. She was a definite drug addict when admitted to the clinic. Eleven years prior to admission, severe pain developed in the right foot, which became blanched and cold. Gangrene of the toes followed, and auto-amputation of all the toes took place within a relatively short time. The following year a similar condition developed in the left foot with auto-amputation of the first and second toes. Secondary vasomotor disturbances with color changes had been present in the feet for at least eight or ten years. One year prior to admission, she had noticed coldness and cyanosis of the fingers of the left hand, especially noticeable on exposure to moderate degrees of cold. During the long course of her illness, talipes equinus of both feet had developed, the deformity being more marked in the right foot than in the left. There was no history of superficial phlebitis. She had smoked from fifteen to twenty cigarettes daily for a number of years.

General examination was essentially negative except for palpable lymph nodes in the inguinal regions and the condition of the extremities. The patient was well developed and well nourished; she weighed 137 pounds (62 Kg.), and was approximately 64 inches (162.6 cm.) in height. Examinations of the urine were entirely negative. The concentration of hemoglobin (Dare) was 70 per cent; the erythrocytes numbered 4,570,000, and the leukocytes, 7,400. The Wassermann reaction of the blood was negative. Roentgenograms of the thorax, the dorsal and lumbar vertebrae and the left forearm and hand were negative. Roentgenograms of the legs and feet disclosed marked atrophy and deformity of the bones of both feet. A biopsy specimen taken from the skin of the left leg showed scar tissue, slight obliterative changes in the vessels, loss of elastic tissue and small deposits of calcium. There was no evidence of tuberculoid structure, and the stain for the bacillus of tuberculosis was negative. Pulsations in the brachial arteries were almost normal; in the radial arteries they were fairly normal; in the right ulnar, they were almost normal, and in the left ulnar, they were absent. Pulsations in both femoral arteries were almost normal, and pulsations could not be detected in the lower extremities below this level. When the feet were elevated, there was pallor, graded 3, of both feet, and with the feet in a dependent position, there was rubor, graded 3. The veins in both feet filled relatively slowly after the feet were placed in a dependent position, indicating a poor flow of blood to the lower extremities. Neurologic examination was objectively negative. The vasomotor

index, which was determined after the intravenous injection of typhoid vaccine, was found to be 2.6 in the right foot, 3.1 in the left foot, 7.1 in the right hand and 8.7 in the left hand.

Because of the marked occlusive vascular disease in the lower extremities and the relatively satisfactory vasomotor indexes, bilateral lumbar sympathetic ganglionectomy was advised. The operation was performed on June 3, 1930. The abdominal vessels appeared to be normal, and complete exploration of the abdominal cavity gave negative results. The patient recovered uneventfully from the operation. Because of vascular insufficiency which was developing in the hands and upper extremities, right and left cervical thoracic ganglionectomy and resection of the trunk were carried out on July 11. At the same time, an attempt was made to correct the deformity of the feet by lengthening the left Achilles tendon and removing a wedge of bone from the anterior outer part of the ankle, which consisted of the head of the astragalus and part of the neck and some of the tarsal bones. A plaster-of-paris cast was applied. Recovery was uneventful.

At the time of dismissal, on August 20, the patient was free from pain in the feet. She had had no recurrence of the lesions of the skin of the legs. A letter from the patient on March 31, 1932, indicated that the progress has not been satisfactory. Pain in the feet had returned, and she was again using morphine for relief.

Case 14.—A married woman, aged 38, of American extraction, registered at the clinic on Oct. 10, 1930, with the chief complaint of pain in the feet, which had been present for approximately eleven months. She had smoked an average of twelve cigarettes a day for fifteen years, and had used alcohol to excess during this time. She had first noticed cyanosis of the left third toe in December, 1929, and about two or three weeks later, severe pain developed in this toe. A similar condition developed in the fourth toe about Jan. 1, 1930, followed by pain and superficial gangrene. Both affected toes were incised and the bone scraped in February. Healing did not follow the operation, and severe pain continued in the left foot up to the time of admission to the clinic. There was no history of superficial phlebitis, and no definite history of intermittent claudication. The patient had lost approximately 20 pounds (9 Kg.) during the course of her present illness, and had been unable to sleep for a greater portion of the time because of the severe pain in the foot. A diagnosis of Raynaud's disease had been made elsewhere.

General examination was negative, except for the condition of the extremities. Repeated examinations of the urine were negative except for slight traces of albumin. The concentration of hemoglobin (Dare) was 78 per cent; the erythrocytes numbered 4,350,000, and the leukocytes, 12,900; the differential count was normal. The concentration of urea was 18 mg. in each 100 cc. of blood. The return of phenolsulphonphthalein was 55 per cent in two hours. The serologic test for syphilis was negative. A fractional test meal showed a free hydrochloric acid of 20, and a total acidity of 38. The phosphorus of the blood was 4.2 mg., and the calcium, 9.1 mg. All of the peripheral arteries in the hands and feet pulsated normally, except the right dorsalis pedis artery, which was closed. When the feet were elevated, there was blanching, graded 3, of the right second, third and fourth toes, and graded 2 of the left fourth and fifth toes. With the feet in the dependent position, there was cyanosis, graded 1 to 2, of the left fourth and fifth toes. There were definite gangrene of the left fourth toe and definite trophic changes in the right second, third and fourth toes and the left fourth and fifth toes. Following an intravenous injection of typhoid vaccine, there was a definite rise in the surface temperature of the various toes. The left first toe showed a rise from 25.3 to

35.6 C. (77.5 to 96 F.). The rise in the right first toe was from 26.8 to 34.5 C. (80.2 to 94.1 F.), and the rise in the right third toe was from 24.8 to 32.6 C. (76.6 to 90.6 F.). The rise in the surface temperature of the left index finger was from 31.9 to 36.5 C. (89.4 to 90.5 F.). The temperature of the mouth rose only 0.6 C. (1.09 F.). The toes were more than 6 C. (10.8 F.) colder than the fingers.

A definite rise in the surface temperature of the toes following injections of typhoid vaccine indicated that there was marked spasm in the collateral circulation, and for this reason, bilateral lumbar sympathetic ganglionectomy was performed on October 18. The second, third and fourth sympathetic ganglions were removed from each side. Recovery from the operation was uneventful. A definite line of demarcation developed in the left fifth toe, and it was finally amputated on November 18. Healing of the wound was delayed, but was complete on December 28.

The postoperative records of the surface temperature of the feet three weeks following operation indicated that a maximal flow of blood to the feet followed bilateral lumbar sympathetic ganglionectomy. On December 22, at normal room temperature, the surface temperature of the right foot ranged from 33.8 to 34.2 C. (92.8 to 93.3 F.), and that of the left foot, from 32.7 to 33 C. (90.8 to 91.4 F.).

Neurologic examination was objectively negative. The blood pressure was 170 systolic and 110 diastolic at the time of admission. Other blood pressure readings, taken twelve days after the bilateral sympathetic ganglionectomy, over a period of twenty-four hours, with the patient at rest, disclosed a range of from 165 to 185 systolic and from 95 to 120 diastolic. Similar readings taken forty days after operation showed a range of from 155 to 210 systolic and from 90 to 125 diastolic.

The results of microscopic examination of vessels from the amputated toe were suggestive of the same occlusive process which we have observed in men with thrombo-angiitis obliterans (fig. 7).

Repeated follow-up letters on this case indicate that the occlusive vascular process in the digits of the lower extremities is still progressive in spite of the bilateral lumbar sympathetic ganglionectomy. Repeated attacks of superficial phlebitis have developed, with severe attacks of pain from time to time in both feet. The pain at certain times resembled that observed in cases of primary erythromelalgia, because elevation of the feet seemed to give relief. This, however, has not been a constant feature in the case. The patient's last letter on March 30, 1932, indicated that the pain in the feet was decreasing, and she has been able to walk for a short time without much discomfort.

Case 15.—A married woman, aged 38, of American extraction, registered at the clinic on Feb. 24, 1931, her chief complaint being numbness and blanching of the fingers, which had been present since childhood, but had become definitely worse two years prior to admission, and the blanching, cyanosis and rubor which originally involved only the tips of the digits had extended back to the first and second joints in both hands. Pain was not associated with the color changes, and trophic changes had not occurred in the skin or subcutaneous tissues. This three-phase color reaction in the hands was precipitated chiefly by exposure to cold, although in the last year she had had a few attacks during the warm weather. There was no history of superficial phlebitis or intermittent claudication.

General examination was essentially negative except for the condition of the extremities. The hands appeared normal when examined in a warm room. Both radial arteries pulsated normally, but pulsation could not be detected in the ulnar arteries. The pulsations in the lower extremities were normal, except the dorsalis pedis arteries, which were reduced approximately 30 per cent. Even after the hands were immersed in hot water for a considerable period, pulsations could not be detected in the ulnar arteries. The hands were later immersed in cold water at 15 C. (59 F.) for a period of fifteen minutes, and the recovery phase of the various

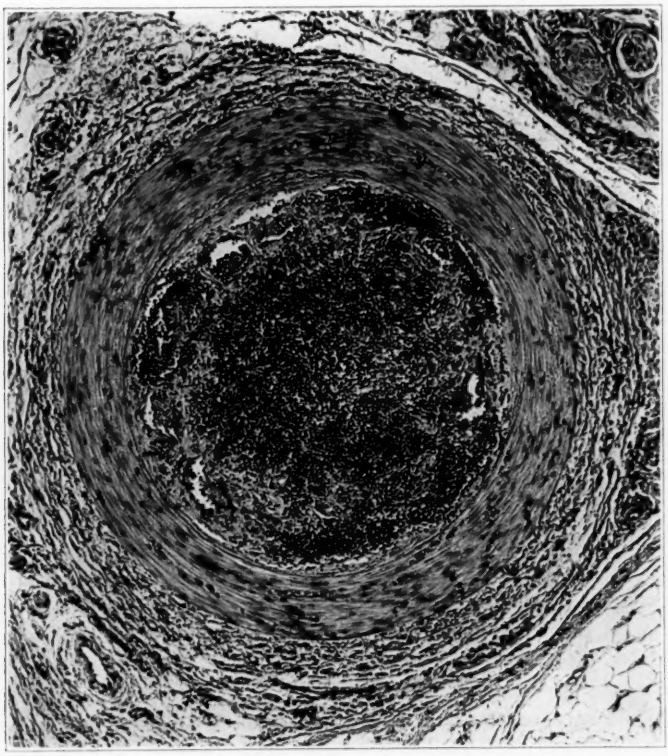

Fig. 7.—Cross-section of a small artery from an amputated toe. The lumen is occluded by an acute thrombus. Hematoxylin and eosin stain; × 85.

fingers was determined separately. Spasm in the vessels could not be induced by this procedure, but there was a decided difference in the recovery of the end of the digits in the right and left hands. The left hand was 2 C. (3.6 F.) warmer than the right. The blood pressure was 135 systolic and 80 diastolic. Examination of the urine was negative. The hemoglobin was 14.4 Gm. for each 100 cc. of blood; the erythrocytes numbered 4,040,000, and the leukocytes, 5,500. The serologic test for syphilis was negative. Roentgenograms of the cervical vertebrae and thorax were negative.

The presence of occlusive vascular disease was conclusive, probably thrombo-angiitis obliterans. Both ulnar arteries were definitely occluded, and this alone was sufficient to rule out Raynaud's disease. The asymmetry of involvement in the hands and the lack of uniform recovery in the digits when exposed to cold are further evidence of occlusive vascular disease.

CASE 16.—An unmarried woman, aged 30, of American extraction, registered at the clinic on Jan. 13, 1932, her chief complaint being daily intermittent pain in the right foot and leg, which had been present for about a year. The pain seemed to be of two distinct types. Almost every morning about 5:30 she had been awakened by cramplike pain in the right foot, associated with a marked blanching of the toes and distal half of the foot. She had obtained prompt relief by immersing the foot in warm water. She also complained of intermittent claudication which developed in the calf of the right leg at the end of about seven or eight blocks of walking. She always obtained prompt relief by resting. The time of the onset of pain varied considerably, depending on the weather. In warm weather she could walk approximately twice as far without discomfort as in cold weather. In the last four months she noted blanching and rubor in the left foot, but actual claudication pain had not developed at the time of her admission. The right foot had remained colder than the left foot for a period of three or four months. The fifth toe of the left foot had been amputated in 1929 because of an infected clavus. Trophic changes had not developed in the lower extremities. The past history was irrelevant except that the patient had smoked twenty cigarettes daily for ten years. There was no history of superficial phlebitis.

Arterial pulsations in the upper extremities were normal. Both femoral arteries and both popliteal arteries pulsated normally, but pulsations could not be detected in the right posterior tibial and dorsalis pedis arteries. The left posterior tibial artery pulsated normally, but only faint pulsations could be detected in the left dorsalis pedis artery. When the feet were elevated 180 degrees, there was pallor of both feet, graded 3; rubor of the right foot, graded 4, and rubor of the distal half of the left foot, graded 1 to 2, were present at 0 degree. Rubor developed much quicker in the left foot than in the right one. At normal room temperature the surface temperature of the right foot varied from 23.6 to 23.7 C. (74.4 to 74.6 F.), and that of the left foot from 22.5 to 22.8 C. (72.5 to 73 F.). The vasomotor index in the right foot was 3.3, and that in the left foot, 5.2. The patient was given intravenous injections of 50,000,000 typhoid bacilli, at which time the vasomotor index was determined. There was a rise in the surface temperature of the right foot from 23.6 to 32.1 C. (74.4 to 89.7 F.), and in the left foot, from 22.5 to 31.7 C. (72.5 to 89 F.). The temperature of the mouth rose from 36.7 to 38.2 C. (98 to 100.7 F.). Arterial pulsations could not be detected in the right foot at the height of the systemic fever, and there were no alterations in the arterial pulsations in the left foot. These data indicate that the patient had organic occlusive vascular disease in the lower extremities, with a large element of spasm in the collateral circulation. Neurologic examination was objectively negative. The blood pressure was 100 systolic and 70 diastolic. The hemoglobin was 14.7 Gm. for each 100 cc. The erythrocytes numbered 5,180,000, and the leukocytes, 12,000. The differential count was normal, and the serologic test for syphilis was negative. Roentgenograms of the thorax, right tibia and fibula and the right foot were negative. Examination of the urine for lead and arsenic gave negative results.

A diagnosis was made of thrombo-angiitis obliterans. Because of the patient's age, the relatively small amount of arterial occlusion in the right foot and the high vasomotor indexes, bilateral lumbar sympathetic ganglionectomy was advised, and this was carried out on January 29. Recovery was uneventful.

This represents an unusually interesting case of thrombo-angiitis obliterans. In considering the relatively mild course which this disease runs in women, we think that the prognosis should be good for the preservation of the extremities. We do not think that there could be any doubt regarding the diagnosis in this case.

CASE 17.—A married woman, aged 39, of English and Dutch extraction, first registered at the clinic on May 25, 1928. For a few years she had noticed gradually increasing nervousness, irritability and symptoms which were interpreted by the examining physician as indicative of nervous exhaustion. Examination revealed a well developed and well nourished woman, 64 inches (162.6 cm.) in height, who weighed 140 pounds (63.5 Kg.). A small adenoma of the thyroid gland was present. The blood pressure was 118 systolic and 80 diastolic. Examination of the urine was entirely negative. The concentration of hemoglobin (Dare) was 70 per cent; the erythrocytes numbered 4,210,000, and the leukocytes, 6,500. The serologic test for syphilis was negative. A roentgenogram of the teeth was negative.

The patient was again admitted to the clinic in an emergency on Feb. 22, 1932. Her past history was irrelevant except that she had smoked from fifteen to eighteen cigarettes daily for a period of fifteen years. She had had no recent infections or illnesses of any type. She had felt perfectly well until 3 a. m. of Feb. 15, 1932, at which time she was awakened by pain in the right hand and forearm. The pain was excruciating. The hand and forearm appeared blanched, cadaveric and devoid of blood. About ten hours later the extremity had splotchy red areas, and in the course of two or three days these became bluish black. The extremity was cold and felt numb. She was unable to move the fingers of that hand. The pain continued and seemed to be of a burning character. Heat was applied in order to increase the flow of blood to the hand and forearm, but this did not serve to eradicate the pain.

General examination was again essentially negative except for the condition of the extremities. The right hand was cadaveric and felt cold, and there was first-stage gangrene of the tips of the thumb and the third, fourth and fifth fingers. Only faint pulsations could be felt in the right brachial artery. Pulsations were entirely absent in the right radial and ulnar arteries. Pulsations were also absent in the left posterior tibial and left dorsalis pedis arteries. All of the other peripheral arteries pulsated normally. The gangrene in the thumb and the third, fourth and fifth fingers gradually extended to approximately the first joint, and definite lines of demarcation developed in the course of four weeks. These grangrenous digits were amputated on March 21, and the patient was dismissed on March 30. The stumps had shown only a slight tendency to heal following the amputations, but there seemed to be a slow although definite increase in flow of blood to the right hand. We believed that the wounds would eventually heal.

At the time of the patient's dismissal pain had practically disappeared. The blood pressure was 124 systolic and 86 diastolic. The heart appeared to be normal. The electrocardiogram showed a rate of 89, sinus arrhythmia, an inverted T wave in derivation III, notched P-waves in derivations I, II and III, an exaggerated P wave in derivation II and slurred Q-R-S complexes in derivations I, II and III.

Repeated examinations of the urine were negative. The hemoglobin was 12.7 Gm. for each 100 cc.; the erythrocytes numbered 4,200,000, and the leukocytes, 13,900. The concentration of urea was 18 mg. in each 100 cc. of blood. Roentgenograms of the thorax and right hand gave negative results. The surface temperature of the right hand at the time of dismissal ranged from 28.7 to 32.3 C. (83.6 to 90.1 F.), which indicated that a fairly adequate collateral circulation had been developed in the involved extremity. The history of sudden arterial occlusion in the right arm strongly suggested an embolic state, but we could find no source for an embolus and are inclined to believe that this patient had a sudden thrombosis, probably at the bifurcation of the brachial artery. The final diagnosis was thrombo-angiitis obliterans.

The onset of sudden arterial occlusion in the right upper extremity, as in this case, is not unusual in cases of thrombo-angiitis obliterans and has been observed rather frequently in our experience. Sudden closures of this type, which involve the popliteal arteries of persons of this age, usually result in gangrene of the foot, and amputation at or above the knee is usually necessary. In this case only the distal joints of four digits were lost. We have never found it necessary to advise amputation of a hand or upper extremity as the result of thrombo-angiitis obliterans.

COMMENT

The most perfect example of the incidence of disease as related to sex is hemophilia. Of the diseases that attack common structures of both sexes, probably those of the vascular system are most common among men. This is seen to some extent in diseases of the coronary arteries, and in arteriosclerosis of the peripheral vessels. In Raynaud's disease, the incidence is much higher among women. Our statistics show an incidence of 9 to 1, and this predominance is significant in the diagnosis of Raynaud's disease. Thrombo-angiitis obliterans, which probably is an inflammatory disease of the arteries and veins due to some infectious or toxic agent, exhibits a similar percentage preponderance in favor of men. This difference in sex could be related to:

1. Some focus of infection peculiar to men. This has called our attention to the possibility of the prostate gland or seminal vesicles as fulfilling this rôle. Our studies have shown that in about 60 per cent of cases of thrombo-angiitis obliterans, prostatitis, graded 2 or more, has been present. No direct causal relationship could be proved between this focus and thrombo-angiitis obliterans.

2. Some endocrine basis peculiar to the male sex which could play a dominant part in the causation of this disease. Proof has not been forthcoming.

3. Tobacco. Several workers (Silbert, Meyer, Weber and Erb) have insisted that tobacco is the etiologic basis of thrombo-angiitis

obliterans. Barker's[7] analysis of the use of tobacco by men in three hundred and fifty cases of thrombo-angiitis obliterans has shown that 3 per cent have never used tobacco, and 20 per cent have used it in small quantities. He has also called attention to the fact that the disease apparently is more serious if tobacco is used freely. Meleney and Miller, Jablons,[8] Koyano and others have reported the cases of patients who were not smokers. If tobacco is an important factor, one would expect a changing incidence of thrombo-angiitis obliterans among women with its increasing use by this sex. In this series of ten cases from the clinic, three patients (cases 13, 14 and 16) used tobacco.

4. There is a premise that women may have the disease in a much milder form, and that the disease is overlooked because of the failure of development of gangrene or the more serious sequelae.

Of the possible explanations, the most logical, in our opinion, is the fourth. In four of our cases the disease was severe enough to produce gangrene. In the remaining cases, the disease had been comparatively mild. These cases might have been easily overlooked if one were not definitely searching for evidence of the disease in the presence of this condition of the extremities. If more women patients were examined as a routine measure for pulsations in the peripheral arteries, the absence of pulsations in one or more vessels, without symptoms, would be found in a certain small percentage. Likewise, the incidence of superficial phlebitis is not rare among women. The question arises, do chronic relapsing forms of superficial phlebitis, which if it occurs among men we have no hesitancy in diagnosing as thrombo-angiitis obliterans, justify this diagnosis of the condition among women? In a certain percentage of these cases of superficial phlebitis one or more arteries are closed (case 9). Unfortunately, our knowledge has not progressed to the point at which the pathologic changes in phlebitis can be accepted as pathognomonic of thrombo-angiitis obliterans. The clinical course of the disease is probably more diagnostic than the pathologic picture. The total number of cases of thrombo-angiitis obliterans which we have studied is slightly less than seven hundred. We found ten cases in which the patients were women. This is an incidence of approximately 1 to 70 (1.2 per cent). Buerger reported two cases in women which were diagnosed clinically. Meleney reported one case in which the patient was a Chinese woman; the pathologic picture and clinical course were typical of the disease. Three of the patients in our series were of Jewish extraction. Their disease was

7. Barker, N. W.: The Tobacco Factor in Thrombo-Angiitis Obliterans, Proc. Staff Meet., Mayo Clin. **6**:65 (Feb. 4) 1931.

8. Jablons, Benjamin: Thrombo-Angiitis Obliterans, Internat. Clin. **3**:193 (Sept.) 1925.

more severe than in the seven Gentiles. A similar clinical impression was gained in our series of men; the disease of the Jewish patients seemed more serious and intense than that in the other races.

CONCLUSIONS AND SUMMARY

Further consideration of this disease, with its predilection for men, should be delayed until a larger number of women with complaints in the extremities have been examined. We are of the opinion that this disease has a higher incidence among women than is brought out by this study. The failure to recognize this is due probably to the facts that the disease is relatively mild among women and the diagnosis is overlooked. If this is a chronic infectious disease, as the work of Buerger [9] and of Horton and Dorsey [10] seems to indicate, no available explanation is at hand.

The ages in the ten cases reported here were 44, 43, 60, 71, 47, 28, 38, 38, 30 and 43, respectively. The average age was 39 years.

Four patients were treated by bilateral lumbar sympathetic ganglionectomy; one of these also had bilateral cervicothoracic sympathetic ganglionectomy. One patient had an amputation of the right leg, and the other patients were treated medically. The treatment, for the most part, has proved satisfactory. The disease among women apparently runs a similar, but definitely milder, course than among men.

The cases of ten women with thrombo-angiitis obliterans observed in the Mayo Clinic are recorded, which represents, so far as we are aware, the first series among women to be placed on record.

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9. Buerger, Leo: Thrombo-Angiitis Obliterans: Experimental Reproduction of Lesions, Arch. Path. **7**:381 (March) 1929.

10. Horton, B. T., and Dorsey, A. H. E.: Experimental Thrombo-Angiitis Obliterans: Bacteriologic and Pathologic Studies, Arch. Path. **13**:910 (June) 1932

MITOTIC MYELOCYTES IN THE PERIPHERAL BLOOD IN A CASE OF MYELOID LEUKEMIA IN A NEGRO

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Indirect or mitotic cell division of nongranular leukoblasts occurs rather frequently in certain types or stages of leukemia. The presence of mitotic leukoblasts in the peripheral blood has been the subject of several recent reports (Dock, Tannhauser, Bowcock and Bishop, Groat, Rabinovici, Bowcock and Dickson).[1] Groat's case showed all stages of mitosis in the peripheral blood, from prophase through telephase to daughter cells; these cells were free from granules.

I am unable to find mention of the occurrence of granular mitotic myelocytes in the peripheral blood, except in the report of Dock. Hirschfeld[2] illustrated mitotic myelocytes in a bone marrow smear. One might question the ability of a cell as mature as a myelocyte to undergo mitotic division.

The following case is of interest because smears from the peripheral blood showed frequent examples of all stages of mitosis in cells containing neutrophilic granules. The case is of further interest because leukemia seems to be rare in our large service for Negroes. In the accompanying series of photomicrographs (figs. 1 to 5), two mitotic erythroblasts from the same case are shown for contrast with the myelocytes.

REPORT OF CASE

History.—A Negro, aged 23, married, a laborer, was admitted to the Grady Hospital, Emory University Service, on April 28, 1932. The complaints were pains in the left leg and abdomen, weakness of the left leg, dizziness, headache and

From the Grady Hospital, Emory University.

1. Dock, George: Mitosis in Circulating Blood, Physician & Surgeon **26**:1 (Jan.) 1904. Tannhauser, S.: Ueber Mitosen im strömenden Blut bei einem Fall von akuter Leukämie, Virchows Arch. f. path. Anat. **264**:391, 1927. Bowcock, H., and Bishop, E. L.: A Case of Acute Leukemia with Unusual Cell Forms in the Blood, Ann. Int. Med. **3**:1252 (June) 1930. Groat, W. S.: Mitosis in Myeloblasts in Peripheral Blood, Am. J. M. Sc. **180**:607 (Nov.) 1930. Rabinovici, E.: Ueber einen Fall von Mikromyeloblastenleukämie mit zahlreichen Mitosen im peripheren Blute, Folia haemat. **43**:132, 1930. Bowcock, H., and Dickson, R. W.: Mitotic Leukoblasts in the Peripheral Blood of a Case of Acute Leukemia, Ann. Int. Med. **4**:1344 (April) 1931.

2. Hirschfeld, H.: Lehrbuch der Blutkrankheiten, Berlin, A. Hirschwald, 1918, plate 3, fig. 38.

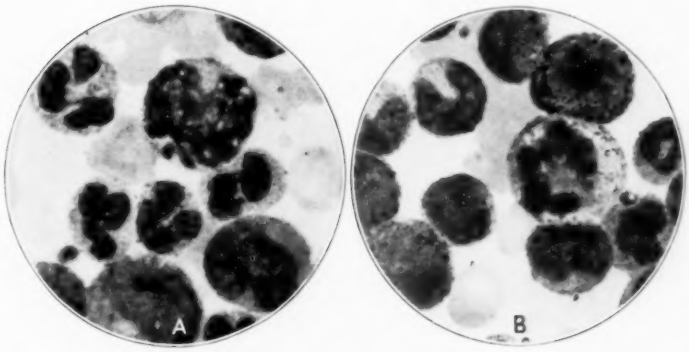

Fig. 1.—Prophase. *A*, preparatory arrangement of chromatin into loose skein. *B*, true monaster; polar view (?); closed skein with definite chromosome formation. Magnification, × 1,100.

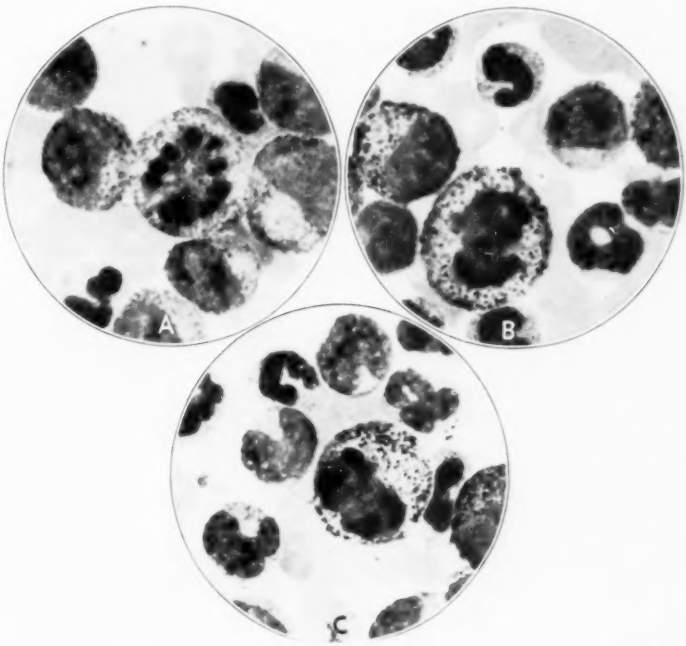

Fig. 2.—Metaphase. *A*, beginning separation of chromosomes; polar view (?). *B*, more definite separation of chromosomes with early diaster formation. *C*, advanced separation of chromosomes to form a definite diaster. Magnification, × 1,100.

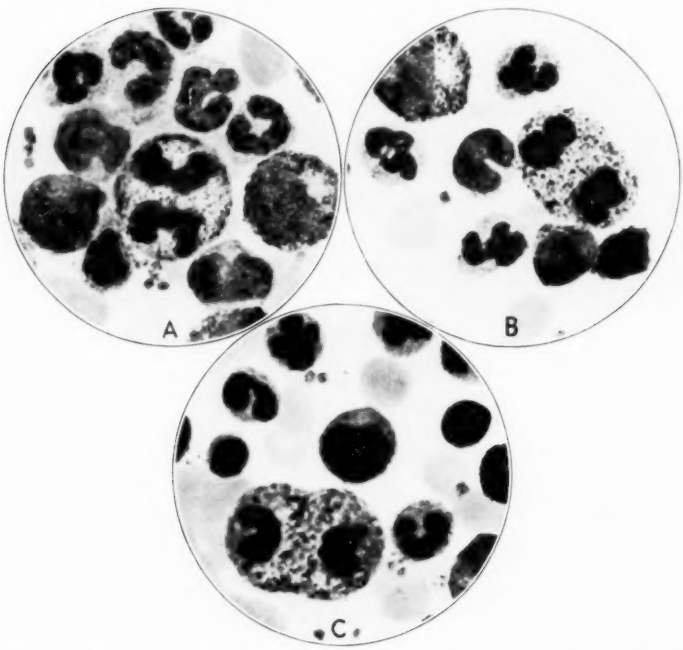

Fig. 3.—Anaphase. *A*, early polar concentration with reassembling of chromosomes. *B*, condensation of chromosomes and beginning separation of cell mass. *C*, slightly later stage (note heavy granulation). Magnification, × 1,100.

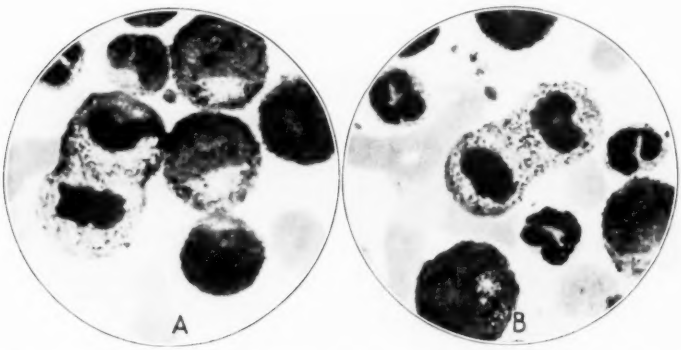

Fig. 4.—Telephase. *A*, beginning equatorial constriction of cytoplasm. *B*, advanced equatorial constriction of cytoplasm and disappearance of identity of individual chromosomes. Magnification, × 1,100.

general weakness. The present illness was said to have started with an injury to the left knee on April 1, 1931. The knee became greatly swollen, but improved sufficiently in five days for resumption of work. A few days later the patient became confined to his bed for a week with a febrile illness diagnosed as influenza. On resuming work he suffered from severe pain in the left groin and pains and weakness in both legs. After an examination of his blood he was given an intravenous injection. This was followed by headache, dizziness, abdominal cramping pains and the vomiting of a large amount of blood. Three days before admission to the hospital he noted a mass in the left side of the abdomen.

His mother had been operated on for cancer of the rectum. The remainder of the family history was unimportant. The patient was the only child. He had had the usual diseases of childhood. He had been confined to bed for seven weeks during 1922 with typhoid fever. He had had gonorrhea during 1924 and 1925 and smallpox during 1926. He had had a cough at intervals for two years, which occasionally produced blood-streaked sputum. During a year there had been an

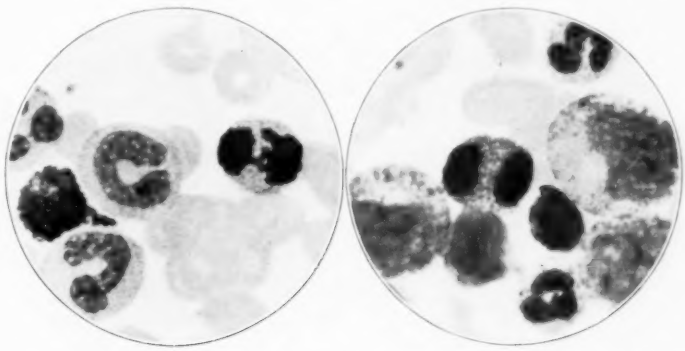

Fig. 5.—Mitotic erythroblasts shown for contrast, with the mitotic leukoblasts in figures 1 to 4. Magnification, × 1,100.

occasional drenching night sweat. For eight months there had been some shortness of breath on exertion. For four months he had vomited frequently immediately after eating. He had been married for six years. His wife was well, but there had been no pregnancies. His highest weight had been 180 pounds (81.8 Kg.) during 1922, and his present weight was about 170 pounds (77.3 Kg.). The remainder of the history was unimportant.

Physical Examination.—The patient was well nourished and well developed and showed no evidence of discomfort. The temperature, pulse rate and respiratory rate were normal. The mucous membranes were pale. There was slight ulceration of the gums with a tendency to bleeding. The tonsils were large. There was enlargement of the superficial cervical, axillary, epitrochlear and inguinal glands. There was bulging of the left side of the abdomen, and in this area there was a palpable, freely movable mass extending from the left costal margin downward to slightly below the umbilicus and from the left flank medially to within 2 cm. of the umbilicus; a notch could be felt, and pressure over the mass produced moderate pain. The edge of the liver was palpable 4 cm. below the right costal

margin in the midclavicular line. There was a small umbilical hernia. A small abscess was found just above the left knee. The remainder of the findings were normal.

Laboratory Examination.—A specimen of urine was normal. The Wassermann reaction of the blood was reported as anticomplementary. The red blood cells numbered 2,200,000 per cubic millimeter. The hemoglobin (Dare) was 50 per cent. The leukocytes numbered 670,000 per cubic millimeter. The blood platelet count was 400,000. In the stained blood smears (Wright's stain) the predominant abnormal cells were classified as neutrophilic myelocytes. Many nucleated red blood cells were present; some of these were seen in the stages of mitotic division. Myeloblasts were rare; an occasional example contained Auer bodies. Lymphocytes were seldom recognizable. Hemohistiocytes and megakaryocytes were seen rarely. The most striking point of interest in the stained smears was the frequent presence of typical stages of mitosis in granular myelocytes. All stages of mitosis were encountered; prophase, metaphase, anaphase and telephase. Eight or ten examples were sometimes encountered in one preparation. The cytoplasm of these mitotic cells appeared to be thin; it took a pale blue stain and often showed a faint ground-glass appearance. The nuclear material stained violet to purple. The cells contained varying numbers of fine and coarse neutrophilic (lilac) granules. Mitotic erythroblasts were much less frequently seen. The cytoplasm of the latter appeared to be thick to the periphery of the cells; it took a slate blue stain and often contained rather coarse dark blue granules. The nuclear material of the erythroblasts was deep bluish purple and had the appearance of being dense.

Roentgen examination of the chest showed a moderate increase in the shadows of the hilus gland. Roentgenograms of the long bones showed no abnormalities.

Course.—The patient was seen at intervals during a period of three months. Two transfusions of 370 cc. and 500 cc. of whole blood produced some improvement of the anemia. Deep roentgen therapy was given seven times at the Albert Steiner Clinic, Grady Hospital. The leukocyte count decreased gradually to 134,000 per cubic millimeter at the last observation; the percentage of myelocytes was usually about 30. During the latter part of the treatment the incidence of mitotic myelocytes was greatly decreased. The patient has moved to a distant city, but is reported to be alive and in fair condition.

The photomicrographs were made by the Photographic Department, College of Medicine, Syracuse University.

GRAPHIC REGISTRATION OF HEART SOUNDS BY THE ARGON GLOW TUBE

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Graphic representation of the auscultatory phenomena of the cardiovascular and respiratory systems, of value to clinician and teacher, has not been widely used because of technical difficulties. The apparatus commonly used has been suited to the physiologic laboratory and not to the office or clinic. The oscillographic records of Einthoven, Lewis, Fahr, Watson and Wemyss, Williams, Wolferth and Hyman, and use of the capsule method by Frank, Wiggers, Broemser, A. Weber and others have thrown considerable light on the physical characteristics and mechanism of the sounds and made more accurate the time relations of heart murmurs. Students of graphic records develop the visual sense in their study of the timing and character of the auscultatory phenomena. They learn to form a visual image of the stethoscopic findings at the time of physical examination. The importance of the stethoscopic findings has recently been properly emphasized by Herrick.[1]

METHOD AND MATERIAL

A method of recording heart sounds, employing some of the newer principles of sound registration, is here briefly reported. In addition, a few representative clinical conditions will be discussed illustrating the sound curves obtained and their significance. The method adapts the argon glow tube to the ordinary electrocardiographic camera to record sound vibrations as light and dark bands simultaneously with the electrocardiogram. These bands are legible even when recorded at camera speeds of 25 or 50 mm. per second. This method appears to answer the requirements of simplicity, low cost, ease of repair through the use of standard parts, constant time relations, superior faithfulness over a wide range of sound frequencies and adaptability to the present electrocardiographic machines. The apparatus is a combination of well tried units, developed by electrical manufacturers for other purposes and described in detail by them. In addition, it records a sound tract that permits later reproduction of the sounds from the film by means of the photoelectric cell. The lack of distortion has been proved by the reproduction of the tones.

A discussion of the microphone and amplifying devices is included, since they are the greatest factors in expense and satisfactory operation. The microphone must be free from distortion and of low threshold to detect the soft murmurs. It should record frequencies even lower than can be heard by the human ear. The

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From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

1. Herrick, J. B.: In Defense of the Stethoscope, Ann. Int. Med. **4**:113 (Aug.) 1930.

condenser type of microphone,[2] attached to the stethoscope chest piece by a rubber tubing of such short length as to avoid resonant effects and time loss, has given good results, and by this arrangement the microphone is placed in the position of the ear in ordinary auscultation.

Any efficient, valve-tube audio-frequency amplifier will give legible results, but it must be very sensitive to react to the low voltage from the microphone caused by the fainter sounds, and must be very stable to introduce no artefacts at low frequencies and during long pauses. The best results have come from well made, three-stage amplifiers of the resistance and large condenser, or battery-coupled types.

The argon tube is caused to glow, i.e., to emit a visible electron stream of high photographic power, by passing through it 350 or more volts at 2 to 5 milliamperes, regulated by a variable 25,000 ohm resistor in series. The same battery supply may be used for the last tube of the amplifier and the glow tube. When the output of the amplifier is impressed on this circuit, remarkable variances in light intensity

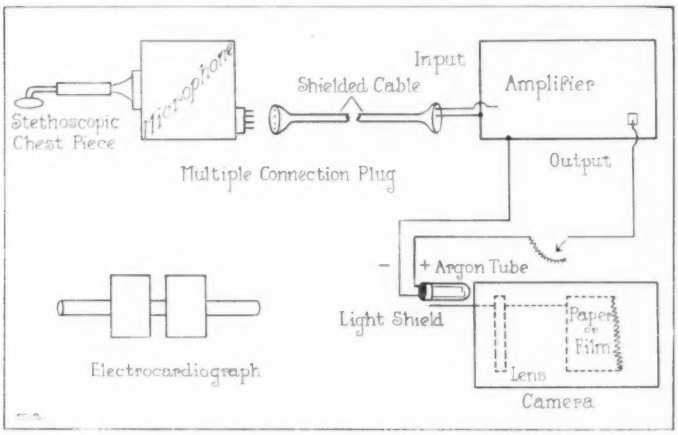

Fig. 1.—Schematic diagram showing apparatus for recording heart sounds.

are produced without afterglow, even when operated at frequencies far above those used in these investigations. A positive current impulse from the amplifier causes a proportionate increase in the brilliancy of the glow and the negative impulse a proportionate decrease in brilliancy; the variations have sufficient photographic power to be registered plainly on moving bromide paper through a slit of 0.2 mm. or less in width. A smaller glow tube, with a more concentrated streak of light, to operate on 250 or less volts and small enough to go inside many of the electrocardiographic camera cases is being tried.

The simplest installation for the present cameras has been to place the argon tube in front of and at one end of the camera slit and to isolate a sound tract from the remainder of the film by use of a thin lead sheet fitted to the inside of the

2. Equally good results, requiring less amplification and expense, may be had by the use of the newer electromagnetic microphone made for the talking picture laboratories. The new Siemers-Halske electromagnetic stethoscope, with a small aluminum plate for direct contact with the chest wall, has proved satisfactory.

camera in a vertical plane. This is cut out to fit around the cylindric lens at 7 or 8 mm. from the end and to extend to the bromide paper. A sheet of thin metal is attached to the outer face of the camera, also in the same vertical plane, and along the inner side of the glow tube, thus preventing the glow from spreading across to the galvanometer portion of the film. Although the cylindric lens concentrates the light to a fairly fine line, better definition is obtained by fitting a copper plate in the sound tract portion so that it presses against the paper. In this plate is cut a horizontal slit 0.2 mm. or less in width and held in the center of the line of concentrated light by support from the camera case. Better optical systems of glass or quartz may be purchased from the sound recording-machine manufacturers. The foregoing is a description of an adaptation for a particular electrocardiographic machine. Each type of camera would need its own design to isolate the sound tract. In the amplifying tube type of electrocardiograph, where the amplifier is built in the same case as the camera, it is necessary to surround the tube and its lead-in wires with metallic shielding.

The apparatus is remarkably stable and easy to handle. There are no delicate strings to protect and adjust. The tube is simply and ruggedly made. It need not be altered in position after once placed. It has a long life, gradually losing photographic power only after several hundred hours of operation. The life of the tube may be prolonged by operating it at a low milliamperage.

The tube is caused to glow by passing more current through it than is later necessary to maintain it. The time required to start the electron stream in the cold tube can be greatly reduced by exposing it to light from a flash light. If a metal shielding is used around the argon tube, a small aperture on top will permit inspection of the evenness of the glow during the silent periods and the cyclic recurrence of the first and second heart sounds, as shown by the flaring and dimming of the glow. This will serve as a check on the correct working of the apparatus before records are taken. The sound tract can be further standardized for lack of distortion and for intensity by recording strips from a known normal heart, or by recording the tone of a tuning fork, or by passing a millivolt from the electrocardiograph's standardizing current through the amplifier. The sound tract can therefore be read not only for its time relations, but also for intensity and frequency or pitch.

The routine here has been to record the three most commonly auscultated points of the precordium, i.e., the second right interspace near the sternum, the third left interspace also close to the sternum and the area of the apex as determined by the point of maximum impulse. These are recorded simultaneously with the first, second and third leads, respectively.

All records have been checked by careful stethoscopic findings and descriptions of the sounds, and where records have been found defective, the cause has generally been due to improper application of the stethoscope to the precordium or to excessive or insufficient amplification.

THE RECORDS AND THEIR INTERPRETATION

The normal tones at the apex are shown in figure 2 as a series of fine, vertical, light and dark bands on the gray tract at the upper border of the electrocardiogram. The first change from the even gray of the silent period, whether it is dark or white, is the initial vibration of the sound. To compare with the string shadow deflections, the dark band corresponds to the portion above the iso-electric line and the white to the portion below. Records taken by this method do not differ from

former records taken by methods which did not introduce distortion. They are comparable in duration, in frequency (as measured by the number of bands per unit of time), as to intensity (as measured by relative degrees of light and darkness of the bands) and as to the time relations between the sounds and the electrocardiograms.

Figure 3 shows the tracings of the sounds at the second right interspace, obtained from a patient with aortic stenosis and auricular fibrillation. The star shows a long, high-pitched, systolic murmur. The second heart sound is almost imperceptible, as is commonly the case in

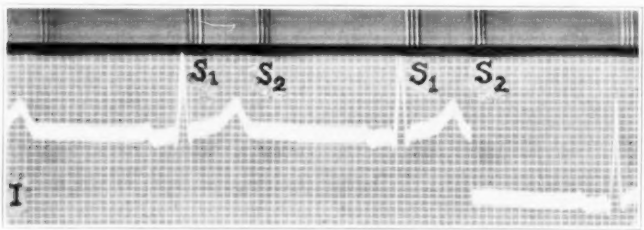

Fig. 2.—The upper tracing shows sound record (apex region) and below it the electrocardiogram (lead I) of a normal subject. S_1 and S_2 are the first and second heart sounds.

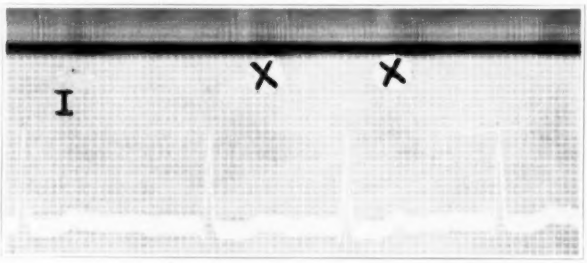

Fig. 3.—The upper sound record shows a prominent systolic murmur from the second right interspace.

aortic stenosis. Figure 4, taken at the third left interspace in the same case as figure 3, shows a premature ventricular beat producing an increased intensity or snapping quality of the first heart sound, which is well indicated in the sound tracing marked by the cross. The circles in the figure point to the presence of a short faint diastolic murmur of aortic insufficiency. The latter part of diastole or presystole was clear. It is necessary to have the patient hold his breath while taking records from the base of the heart to avoid the interference of respiratory sounds.

In figure 5 are shown the tracings of a patient with mitral stenosis and auricular fibrillation, before and after regularization by quinidine. The sound tracings were obtained at the region of the apex. The point marked *X* in the upper tracing shows a presystolic interval without a

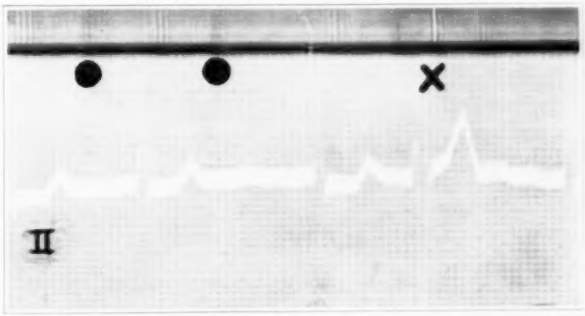

Fig. 4.—The sound record from the third left interspace shows at the circles a short, faint diastolic murmur, and the *x* indicates an accentuation of the first heart sound from a premature beat. The patient had aortic stenosis and insufficiency.

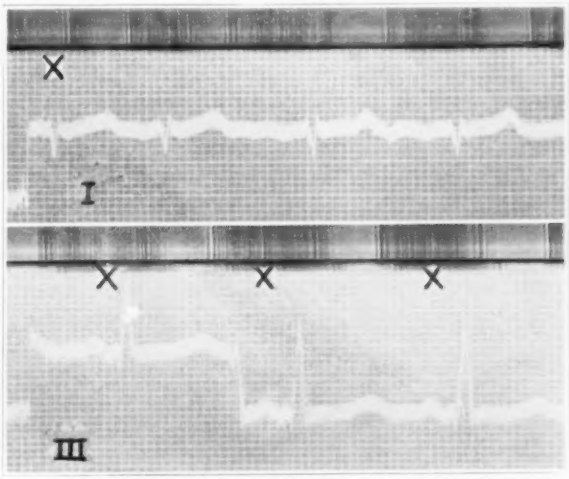

Fig. 5.—Sound records from a case of mitral stenosis and auricular fibrillation. The upper record shows a clear interval in presystole marked *X*. The lower record, made with the heart regularized by quinidine, shows a constant presystolic murmur marked *X*.

murmur. This occurred only in the longer pauses. In the lower tracing, when the heart rhythm was regular after the administration of quinidine, the presystolic murmur was always present as shown at the times marked *X*.

The sound record shown in figure 6 was taken at the third left interspace of a patient with active rheumatic carditis. It shows a greatly accentuated second heart sound, marked S_2. A short, high-pitched murmur follows this sound, the clinical significance of which was difficult to determine. The P-R interval in this case was 0.25 second.

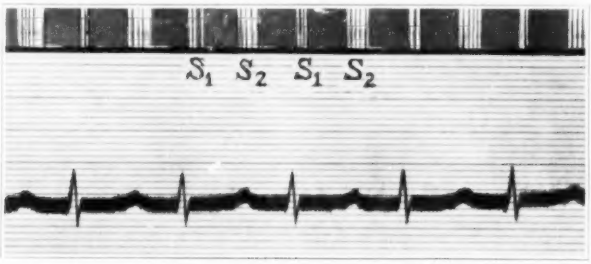

Fig. 6.—Note the accentuation of the second heart sound followed by a short diastolic murmur.

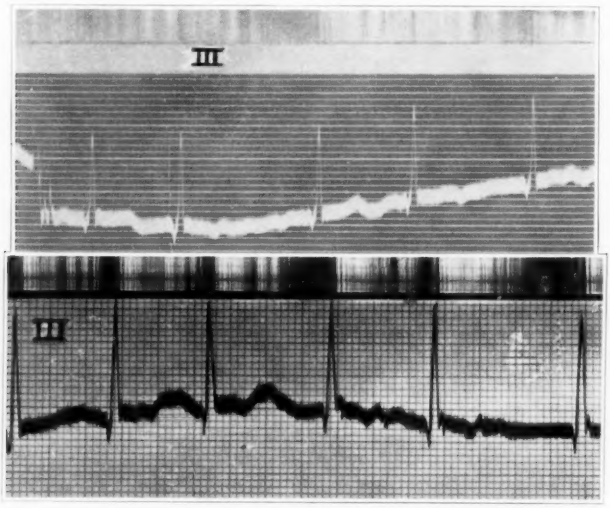

Fig. 7.—The upper record shows the murmurs of mitral stenosis and auricular fibrillation before cardiolysis and the lower record, after cardiolysis. Note the increase in intensity of the diastolic murmur after the ribs were removed.

Figure 7 illustrates the apical sounds in a case of decompensated mitral stenosis with auricular fibrillation. The systolic and diastolic murmurs are loud and long, the systolic lasting up to the diastolic and the diastolic running through varying portions of diastole, the presystolic period being clear in the longer diastolic intervals.

The lower tracing was taken one month after cardiolysis, following which marked subjective and objective improvement took place. The cartilaginous and bony structures were gone, and these sounds were recorded through the thin, heaving precordium by allowing a Bowles type of chest-piece to rest by its own weight on the precordium, the heaving thrust of the heart being thus largely eliminated. Under such circumstances the resulting sounds must closely resemble the intrinsic vibrations of the wall of the heart as if the exposed heart were directly auscultated. Little change in the diastolic murmur was noted.

Experience with the patient represented by figure 8 proved rather instructive. The patient was a man, admitted to the hospital for paroxysmal dyspnea and congestive heart failure. His chest was emphysematous and filled with "noisy" râles, making auscultation difficult. At that time, a faint protodiastolic gallop was heard at the apex,

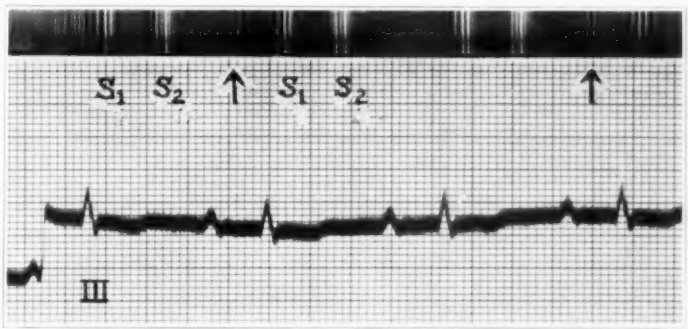

Fig. 8.—In the sound record the arrows point to a definite late diastolic murmur which was interpreted clinically as a gallop rhythm.

but at the time of the sound record, therapy had slowed the heart and the gallop was termed late diastolic. A tentative diagnosis of myocardial deficiency without valvular disease was made. The patient had, however, the mitral facies, and the electrocardiogram showed right axis deviation and wide, notched P waves. In this case the sound records proved valuable, in that a definite murmur was detected in late diastole, which, in time, was related to auricular systole.[3] This suggested the possibility of mitral stenosis, and on subsequent clinical examination when the chest was clearer and auscultation more satisfactory, this murmur was more distinct and sufficiently characteristic to warrant the diagnosis of mitral stenosis. In this instance, the sound tracings proved to be helpful at a time when, from clinical examination alone, a wrong interpretation might have been made.

3. Wolferth, C. C., and Margolies, A.: Various Types of "Extra" Heart Sounds, M. Clin. North America **14**:897 (Jan.) 1931.

The foregoing method of recording sounds has also been used to photograph the qualities of the first heart sounds in the presence of complete heart block with and without auricular fibrillation. In the former, the first sound was found to vary in different cycles and in the latter, it was found to be constant. The ease with which it may be employed in any electrocardiograph laboratory permits its use to testify as to the presence and character of a murmur in disputed diagnosis or insurance examinations. It also offers a method of further investigating the whole subject of gallop rhythm and other auscultatory phenomena met with in general medicine, such as cranial bruits, fetal heart sounds and arteriovenous murmurs.

CONCLUSIONS

A new method for photographing heart sounds has been described, the argon glow tube being used. Once the necessary apparatus was set up, the method was found to be simple. It could detect the ordinary and obscure heart sounds.

Illustrations of some of its uses in clinical cases are described and suggestions for its further applications are offered.

AZOTEMIA DUE TO LOW BLOOD PRESSURE

ITS OCCURRENCE IN AN UNUSUAL CASE OF ACUTE RHEUMATIC FEVER

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BOSTON

The occurrence of azotemia in the absence of nephritis is recognized and has been discussed extensively in the literature. Little attention, however, has been paid to the possibility of nitrogen retention in the blood being due primarily to anuria resulting from hypotension. Both Roch [1] and Merklen [2] in their papers on the subject call attention to anuria or oliguria as a frequent extrarenal cause of azotemia, but they do not mention hypotension among the causes for this oliguria. Azotemia due to hypotension appears to be a rare occurrence, or else blood studies with this point in mind have not been made in cases of marked hypotension. It seems probable that the latter is the case.

Studies [3] on the physiology of the kidney have shown that in the experimental animal a minimum blood pressure of from 30 to 40 mm. of mercury is necessary for the secretion of urine. This figure corresponds remarkably to the osmotic resistance of the blood proteins in man, calculated at 30 mm. by Starling in 1899. For this reason, it has been assumed that the minimum blood pressure required for urinary secretion is in man also from 30 to 40 mm. Clinical evidence on this point is quite meager, but it seems reasonable to suppose that as the blood pressure approaches or reaches this minimum level, there will result oliguria or anuria, which if maintained for any length of time will cause nitrogen retention in the blood. Müller-Deham [4] in 1922 presented clinical evidence of diminished kidney function in even relatively mild cases of hypotension. He studied cases of Addison's disease, carcinoma of the stomach and duodenal ulcer in which the blood pressure ranged between 60 and 105 systolic, and found the kidney function definitely impaired, as judged by urinary volume and power of concentration. He does not include blood studies in his paper.

From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Roch, M.: L'azotémie sans lésions rénales, Rev. méd. de la Suisse Rom. **50**:497 (July) 1930.

2. Merklen, P.: Médecine **3**:760 (July) 1922.

3. Cushny, A. R.: The Secretion of the Urine, New York, Longmans, Green & Company, 1917, p. 107.

4. Müller-Deham, A.: Klinische Beobachtungen über Nierenfunction und Blutdrücksenkung, Wien. Arch. f. inn. Med. **3**:323, 1922.

There are two clinical conditions in which one might expect to find nitrogen retention resulting from hypotension. These are shock, medical or surgical, and, perhaps, Addison's disease.

Duval and Grigaut [5] in 1918 studied chemical analyses of the blood in cases of traumatic shock of varying intensity and duration in which the blood pressures ranged from 50 to 80 systolic and from 30 to 50 diastolic. They found the blood urea nitrogen and nonprotein nitrogen elevated, but only moderately so, hardly exceeding twice the normal figures. This elevation was interpreted as being due to the liberation of nitrogenous materials from the traumatized tissues. Aub and Wu [6] in 1920 found only slight elevation of blood urea in experimentally produced traumatic shock in cats, and control animals in which a corresponding lowering of blood pressure was produced by intrapericardial pressure showed no elevation of blood urea. Garofeanu and Lazar [7] in 1926 studied the blood urea of dogs in peptone shock, samples of blood being withdrawn from twenty to thirty minutes after the establishment of shock, and found a slight increase in a few cases, but a definite decrease in most cases. This decrease they considered as probably due to the loss of the plasma which carries the main part of the urea into the tissues. The failure to find a marked azotemia in these instances of traumatic shock may be due to the fact that the blood pressure did not fall sufficiently low or else had not remained low for a sufficient period before the blood analyses were made.

The occurrence of shock in certain medical conditions was demonstrated by Janeway [8] in 1907 and more recently by Atchley [9] in 1930. The latter pointed out the associated inhibition of renal function, and in the report of one of his cases he mentioned a rapid rise in the blood urea nitrogen following the establishment of anuria. Evans [10] recently reported the occurrence of azotemia in a patient who on the sixth day after an operation for appendical abscess went into a state of circulatory collapse, which persisted intermittently, with the blood pressure falling as low as 50 systolic, for approximately fourteen hours before death. Although the nonprotein nitrogen rose to 240 mg. per hundred cubic

5. Duval, P., and Grigaut, A.: L'intoxication par les plais de guerre; La rétention azotée des blessés, Compt. rend. Soc. de biol. **81**:873, 1918.

6. Aub, J. C., and Wu, H.: Studies in Experimental Traumatic Shock, Am. J. Physiol. **54**:416 (Dec.) 1920.

7. Garofeanu, M., and Lazar, N.: Les variations de l'urée sanguine au cours du choc peptonique chez le chien, Compt. rend. Soc. de biol. **95**:427 (July) 1926.

8. Janeway, T. C.: Some Common Misconceptions in the Pathological Physiology of the Circulation and Their Practical Significance, New York M. J. **85**: 193, 1907.

9. Atchley, D. W.: Medical Shock, J. A. M. A. **95**:385 (Aug. 9) 1930.

10. Evans, T. S.: Azotemia with Normal Kidneys Found Post Mortem; Possible Cause: Low Blood Pressure After Operation, Arch. Int. Med. **48**:1231 (Dec.) 1931.

centimeters, postmortem examination revealed essentially normal kidneys, so it was thought most probable that the renal insufficiency had been due to hypotension.

It has been shown by several observers that experimental extirpation of the renal glands is followed by a marked rise in blood urea nitrogen without evidence of nephritis. Marshall and Davis,[11] in 1916, found no relation between this nitrogen retention and the blood pressure level, and concluded that hypotension was not an important factor in this azotemia, but that the adrenals must normally exert a favorable influence over the function of the kidneys. Nitrogen retention in cases of Addison's disease has been a frequent observation, and this occurrence in the absence of nephritis has given rise to considerable speculation and study. Sicard and Haguenau[12] in 1914 reported blood nonprotein nitrogen values of 245 and 200 mg. per hundred cubic centimeters in two cases of Addison's disease in which the urine showed no evidence of nephritis and in one of which autopsy revealed no appreciable renal lesions. Rowntree,[13] in 1925, studied the renal function in twelve cases of Addison's disease and found the blood urea nitrogen elevated above 30 mg. in ten cases, above 50 mg. in four cases and between 90 and 100 mg. in two cases. Although the phthalein excretion was normal in all but two cases, additional evidence of renal insufficiency was shown by a diminished urinary output. The urine in these cases was essentially normal, and postmortem examination in several showed no evidence of nephritis. The blood pressure in these cases averaged 90 systolic and 62 diastolic, the lowest readings being 60 systolic and 40 diastolic. Rowntree ventures the opinion that ". . . since organic pathological evidence is usually lacking, diminished renal function is probably an accompaniment of the low blood pressure and the resulting circulatory disturbance." Mozer[14] in 1929 reported three cases of azotemia in Addison's disease with blood nonprotein nitrogen readings of 260, 80 and 79 mg. per hundred cubic centimeters, all of which had negligible urinary findings and showed essentially normal kidneys at autopsy. Mozer feels that hypotension alone cannot account for the renal insufficiency in these cases, basing this contention on the fact that there was no appreciable oliguria in his three cases and on the fact that transient hypotension in acute infectious conditions is frequently not accompanied by evidence of renal insufficiency. He cites a case of chronic hypotension (from 65 systolic and

11. Marshall, E. K., Jr., and Davis, D. M.: The Influence of the Adrenals on the Kidneys, J. Pharmacol. & Exper. Therap. **8**:526 (Sept.) 1916.

12. Sicard, J. A., and Haguenau: Dosage de l'urée sanguine des addisoniens, Bull. et mém. Soc. méd. d. hôp. de Paris **37**:902, 1914.

13. Rowntree, L. G.: Studies in Addison's Disease, J. A. M. A. **84**:327 (Jan. 31) 1925.

14. Mozer, J. J.: De l'influence de la surrénale sur le fonctionnement du rein; syndrome azotémique addisonien, Presse méd. **37**:156 (Feb. 2) 1929.

30 diastolic to 70 systolic and 40 diastolic) in a girl with an endocrine disturbance who showed a normal blood urea nitrogen and a normal phthalein excretion. He concludes, in accord with Marshall and Davis,[11] that there must be a suprarenal influence on renal function without which the kidneys fail to perform their work properly.

The following case is of interest in that it presents the same phenomenon noted by Evans,[10] but with recovery, and because it represents what seems to be a manifestation of acute rheumatic fever of unusual severity

REPORT OF A CASE

History.—On July 30, 1931, an Italian-born laborer, aged 23, was brought to the medical clinic of the Peter Bent Brigham Hospital in a stuporous condition with a history of vomiting for five days accompanied by fever and pains in the joints. He had previously been in good health, with no history of disease or exposure to industrial poisons, and had been taken ill rather suddenly while at work with a road construction gang.

Examination.—On admission, he presented the picture of extreme circulatory collapse. He was apathetic, though somewhat restless, and could be partially roused only with difficulty. The extremities were cold and cyanotic; the radial pulse could not be felt, and no blood pressure reading could be obtained. The heart sounds were faint, quite rapid (140) and tic-tac in quality, and there was a pericardial friction rub in the pulmonic region. There were no demonstrable cardiac enlargement and no peripheral edema or congestion of the lungs. The temperature was 100 F. by rectum and the respiratory rate, 35. The patient was markedly dehydrated, as evidenced by a red blood cell count of 7,000,000 with a hemoglobin of 125 per cent (Sahli), and there was a leukocytosis of 24,000 with 83 per cent polymorphonuclears. Although he had last voided about five or six hours before admission, catheterization yielded only 5 cc. of clear urine, which on analysis showed the slightest possible trace of albumin but no cells or casts.

An electrocardiogram showed normal curves; a lumbar puncture gave normal findings; the Wassermann and Hinton tests of the blood were negative, and two blood cultures were negative.

Course.—The patient vomited only once after admission, but in spite of the fact that he retained considerable amounts of fluid by mouth, he was given during the first thirty-six hours tap water by rectal drip, 3,000 cc. of Ringer's solution by clysis and 100 cc. of 50 per cent dextrose intravenously. At the end of this period his condition remained essentially unaltered; the blood pressure was still not recordable, and there was almost complete anuria demonstrated by a second catheterization yielding but 4 cc. of urine, which like the first showed a slight amount of albumin but no red cells or casts. A blood urea nitrogen determination at this time showed 75 mg. per hundred cubic centimeters.

On the third day, following a clysis of 1,500 cc. of Ringer's solution accompanied by 50 cc. of 50 per cent dextrose intravenously, there was striking clinical improvement; the cyanosis disappeared, a weak pulse could be felt at the wrist, and the blood pressure was obtained for the first time, with a reading of 100 systolic and 80 diastolic. Five hundred cubic centimeters of urine was passed, which showed in addition to a slight trace of albumin a few red blood cells (from 1 to 2 per high power field), but no casts.

In spite of progressive clinical improvement and a good urinary output, a second blood urea nitrogen determination on the fifth day showed a rise to 119

mg. per hundred cubic centimeters. It then gradually fell to normal, reaching 65.8 mg. on the eighth day and 12.6 mg. on the twelfth day. The urine gradually cleared, becoming entirely normal on the fifteenth day and remaining so for the remainder of the period of observation. The phenolsulphonphthalein excretion was slightly depressed (25 per cent) on the fifth day, but subsequent determinations were normal (from 40 to 65 per cent). Further blood studies on the eighth day showed a carbon dioxide-combining power of 60.7 per cent by volume, and the blood sodium chloride to be 350 mg. per hundred cubic centimeters.

The temperature dropped to normal on the third day, but on the fifth day again rose, reaching 102.5 F. on the sixth day, when there appeared a generalized morbilliform rash, bright red, macular, nonitching and evenly distributed over the whole body, including the palms and the soles. The eruption became largely confluent and faded out entirely in the course of a week. The temperature again subsided, but continued to be slightly elevated up to the time of the patient's discharge on the thirty-ninth day after admission. The leukocytosis continued, reaching 33,000 on the eighth day and gradually dropping to 18,000 on discharge. The pericardial rub disappeared several days after admission, and on discharge the heart sounds were normal, except for a slight, persistent tachycardia.

The patient was seen four months later, and although apparently in the best of health, still showed a tachycardia of from 90 to 110 and a leukocytosis of from 16,000 to 18,000.

COMMENT

The fever and leukocytosis, with the absence of a history of poisoning indicated some sort of an infection, while the history of transient joint symptoms, the pericardial rub, the morbilliform rash and the subsequent chronicity of the infection, all pointed to acute rheumatic fever.

It seems justifiable to assume that azotemia occurred in this patient in the absence of nephritis, the scant urinary findings being due to the general toxic reaction with simple cloudy swelling of the tubular epithelium. However, the nitrogen retention was probably not due to the marked hypotension alone. Blum [15] has called attention to the rôle of a lowered sodium chloride level in the blood in the production of the azotemia seen in cases of persistent vomiting or diarrhea. He explains this nitrogen retention as being a defense reaction to maintain the proper molecular concentration of the blood. With the history of persistent vomiting prior to admission and the lowered blood sodium chloride level a week after admission, this factor doubtless played a part in the production of the azotemia in this case. However, the marked rise in the blood urea in spite of the administration of large quantities of Ringer's solution by clysis and in the absence of further vomiting indicates that the anuria of hypotension was probably the main factor in this nitrogen retention.

15. Blum, L.; Grabar, P., and van Coulaert: L'azotémie par manque du sel; son mécanisme, Ann. de méd. **25**:34 (Jan.) 1929.

CHRONIC ARTHRITIS

A CLINICAL ANALYSIS OF THREE HUNDRED AND FIFTY CASES

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In considering any study of arthritis it seems advisable to define the term as used, as it obviously means different things to different persons. My conception of arthritis is that it is a disease probably of infectious origin. Etiologic evidence is accumulating which points strongly toward the streptococcus as being the causative agent in the majority of cases of arthritis, including acute cases that are termed rheumatic fever as well as chronic arthritis. The literature covering the etiologic evidence for streptococcic infection has been reviewed by Clawson [1] for rheumatic fever and by Clawson and me [2] for chronic arthritis. Jordan [3] and Poynton and Schlesinger [4] have also reviewed the literature of the microbic origin of these conditions. There is no doubt but that other organisms such as the gonococcus and Bacillus tuberculosis may produce a type of arthritis that occasionally simulates streptococcic arthritis. It is also known that other organisms, such as the pneumococcus, staphylococcus, dysentery bacillus, typhoid bacillus and probably the spirochete, are causative in occasional cases. The evidence would signify, however, that a high percentage of all cases of acute and chronic arthritis are due to streptococcic infection. The exact nature of this infection has not been entirely clear, some investigators contending that the organic changes in the joints might be due to an allergic reaction alone and not to the presence of actual bacterial invasion. From recent investigations it seems more likely that streptococcic arthritis is dependent on the actual presence of organisms, and that the allergic or hypersensitive factor is of secondary importance. It is apparent that the clinical and pathologic manifestations of strepto-

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1. Clawson, B. J.: Bacteriology of Acute Rheumatic Fever with an Experimental Basis in Animals for Vaccine Therapy, Minnesota Med. **14**:1, 1931.

2. Clawson, B. J., and Wetherby, Macnider: An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with a Summary of Results Obtained in Patients, Ann. Int. Med. **5**:1447, 1932.

3. Jordan, E. P.: The Microbic Etiology of Rheumatic Fever and Arthritis, Arch. Path. **10**:79 (July) 1930.

4. Poynton, F. J., and Schlesinger, B.: Recent Advances in the Study of Rheumatism, Philadelphia, P. Blakiston's Son & Co., 1931.

coccic arthritis may present many variations dependent on secondary factors, such as age, climate, trauma, exposure, individual susceptibility and resistance, the virulence of the organism and the extent of the inciting infection. Rolleston [5] has expressed the following opinion:

> On the whole, it might be reasonable to suggest that varying degrees of diminished constitutional resistance of the fibrous tissues or sensitization to infection on the one hand, and on the other hand, the action of different kinds of streptococci might explain the different clinical manifestations seen among the diseases grouped for convenience under the head of rheumatism.

The terminology in use for arthritis has been a subject of confusion, owing to the absence of an accepted etiologic classification. The classifications generally used are that of Garrod [6] adopted by the British Ministry of Health and those of Goldthwait [7] and Nichols and Richardson: [8]

Classifications of Arthritis

British	Goldthwait	Nichols and Richardson
I. Rheumatic Fever		
II. Rheumatoid	Infectious / Atrophic	Proliferative
III. Osteo-arthritis	Hypertrophic	Degenerative

The preceding classifications are not in true corollary groups because of the different criteria for selection. Nichols and Richardson's study was made on a pathologic basis, without regard to the etiologic nature. They recognized similar pathologic changes produced by different agents. Goldthwait has included gonorrheal arthritis under the infectious group. The British classification has dealt with only so-called nonspecific arthritis. Using the terminology of the British classification, I concur with Cecil [9] in the opinion that the cases of clinical rheumatoid arthritis are due to streptococci. The term osteo-arthritis has apparently been used to cover conditions with various causes. Unfortunately, some clinicians use this term to include senescent changes, pure traumatic damage in the joints and changes produced by articular hemorrhage from purpura or hemophilia. I believe that most of the cases with pains of the joints, clinically termed osteo-arthritis are only variations

5. Rolleston, H. D.: Rheumatic Diseases, Lancet **2**:1016, 1928.

6. Garrod, A. E., in Albutt, T. C., and Rolleston, H. D.: A System of Medicine, New York, The Macmillan Company, 1910, vol. 3, p. 3.

7. Goldthwait, J. E.; Painter, C. F., and Osgood, R. B.: Diseases of the Bones and Joints, Boston, D. C. Heath & Company, 1909.

8. Nichols, E. H., and Richardson, F. L.: Arthritis Deformans, J. M. Research **26**:149, 1909.

9. Cecil, R. L.; Nicholls, E. E., and Stainsby, W. J.: The Etiology of Rheumatoid Arthritis, Am. J. M. Sc. **181**:12, 1931.

of streptococcic arthritis, largely in older persons in whom chondro-osseous changes predominate, and that there is not a sharp line of distinction between such cases and those termed rheumatoid arthritis. Clawson [10] has isolated streptococci from the blood and subcutaneous nodules of older persons with predominant hypertrophic changes that might be termed osteo-arthritis according to the popular clinical and roentgenologic criteria of differentiation. McCrae [11] and Timbrell Fisher,[12] on the basis of clinical and pathologic studies, have expressed the opinion that a high percentage of persons with chronic arthritis have involvement of the mixed type. Fisher, in 1928, prior to much of the recent etiologic investigation, advised the use of the general term chronic arthritis. McCrae has stated his inability to place patients in two distinct clinical groups. With the aforementioned considerations in mind, a clinical analysis has been made of 350 consecutive cases of arthritis seen in the outpatient department of the University of Minnesota Hospital during the past year. The patients were admitted chiefly for intravenous streptococcic vaccination, which has been discussed in previous papers.[13] No selection of patients was made other than that those chosen had had nontraumatic pain in the joints for at least two months, and no one was included who gave clinical evidence of a specific type of infection such as gonorrhea or tuberculosis. Relatively few cases of such types were met with in this series. The material represents a clinical cross-section of that large group of conditions sometimes termed nonspecific arthritis. Muscular pain was not infrequent in this group, and in the patients with more serious involvement, the articular condition was apparently only a prominent local manifestation of a constitutional disease. As a routine, a record was made in every instance to obtain information concerning sex, present age, age at onset, duration, history of probable streptococcic infections, trauma as an inciting factor, previous therapy, joints involved, the first joint or joints involved, the joints most severely involved, the degree and type of articular involvement, roentgen studies, observations on the heart and possible associated conditions. In the last 300 cases, a thorough routine search was made for subcutaneous nodules.

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10. (*a*) Wetherby, Macnider, and Clawson, B. J.: Chronic Arthritis, with Special Reference to Vaccine Therapy, Arch. Int. Med. **49**:303 (Feb.) 1932. (*b*) Clawson, B. J., and Wetherby, Macnider: Subcutaneous Nodules in Chronic Arthritis, Am. J. Path. **8**:283, 1932.

11. McCrae, T., in Osler, W., and McCrae, T.: Modern Medicine, Philadelphia, Lea & Febiger, 1915, vol. 5, p. 895.

12. Fisher, A. G. Timbrell: Chronic (Non-Tuberculous) Arthritis, New York, The Macmillan Company, 1929.

13. Clawson and Wetherby.[2] Wetherby and Clawson [10a]; Intravenous Streptococcic Vaccine Therapy in Chronic Arthritis, J. A. M. A. **98**:1974 (June 4) 1932.

CLINICAL FINDINGS

Sex Incidence.—In the series of 350 persons, 240 were women (68.57 per cent) and 110 were men (31.43 per cent). It is of interest that during this period the sex ratio of patients admitted to the outpatient department was approximately 57 per cent women and 43 per cent men. Most of the patients in our series came definitely for intravenous streptococcic vaccine therapy, so that the sex difference of the total admissions to the dispensary is hardly applicable in explaining the marked preponderence of females among arthritic patients. The possibility was considered that women might seek relief for less severe symptoms than men. On careful analysis this does not seem to be the case, as the duration of symptoms was determined and found to be about the same for the two sexes. A similar preponderance of females has been found in large series of cases by the Cambridge Committee,[14] Garrod,[15] Llewellyn Jones,[16] Cecil and Archer[17] and Pemberton and Pierce.[18] McCrae,[11] however, found no marked difference in incidence in the two sexes.

Age of Patients.—In considering the age of arthritic patients, it has seemed advisable to determine both the age at onset and the age at the time of admission to the hospital. This has been done for men and women separately; no striking differences between the two sexes has been found, the peak for both appearing in the fifth decade when the age of onset is considered and about evenly divided between the fifth and sixth decades when the present age is considered. Pemberton and Pierce[18] and Garrod[15] also found the peak of onset to occur about as in this series. In McCrae's[11] series the peak of onset was in the third and fourth decades.

Duration of Arthritic Symptoms.—The duration of articular symptoms in men and women was determined separately and in a total group. There was found to be no marked difference in the duration of arthritis in the two sexes at the time of admission to the outpatient department. It is of interest that 55.2 per cent of the total group had had arthritic symptoms more than five years before admission to the hospital, and that only 12.3 per cent had had a history of less than one year's duration.

14. Cambridge Committee Report, cited by McCrae (footnote 12, p. 899).

15. Garrod, A. E.: A Treatise on Rheumatism and Rheumatoid Arthritis, London, Charles Griffen Company, London, 1890.

16. Jones, R. Llewellyn: Arthritis Deformans, New York, William Wood and Company, 1909.

17. Cecil, R. L., and Archer, B. H.: The Classification and Treatment of Chronic Arthritis, J. A. M. A. **87**:741 (Sept. 4) 1926.

18. Pemberton, Ralph, and Pierce, E. G.: A Clinical Study of Chronic Arthritis Based on Eleven Hundred Cases, Am. J. M. Sc. **173**:31, 1927.

Incidence of Distribution of Involvement in Various Joints.—There are many popular clinical impressions in regard to the details of involvement of the joints in chronic arthritis. Garrod [15] and Pemberton and Pierce [18] have previously tabulated the incidence of involvement of the individual joints.

In this series a detailed routine history of pain in the joints was taken in each case. A joint was considered to be involved if it had been the location of pain at some time during the course of the disease. The incidence of monarticular or polyarticular involvement was determined, and it was found that only 5 patients of a total of 350 had involvement of a single joint. In a small percentage of cases the symptoms were predominant in a single joint, but the condition could not be strictly interpreted as one of monarticular involvement.

The average number of joints involved in a patient was determined for men and women separately, the spine, fingers, toes, hands or feet of one side being counted as only one joint. There was no striking difference in the total number of joints involved for the two sexes; in women the average was 10.9 joints for each patient, and in men, 10 joints.

In the great majority of patients the involvement of the joints was bilaterally symmetrical in distribution, but not necessarily of equal degree on both sides. The relative distribution of the involvement in men and women was determined separately and in a composite group. It was noted that in both sexes the knees were more commonly affected than any other joints, there being involvement of the knee in 290, or 82.8 per cent, of the entire group of 350 persons. The fingers were next most commonly involved in the total group, being affected in 61.1 per cent of the cases.

There was a difference between the two sexes in the incidence of involvement of joints. The percentage of involvement of individual joints in the two sexes is given in table 1.

In the women there was a significant predominance over the men of involvement of the fingers, hands and toes; while in the men there was relatively more frequent involvement of the feet, hips and spine. The cervical part of the spine was more frequently mentioned as being involved than any other portion.

The incidence of joints initially involved was determined for men and women separately. The patients sometimes mentioned more than one joint as being involved at the onset. If only two joints were mentioned, they were recorded separately. If three or more joints were mentioned, the initial involvement was expressed as multiple. The knees were the first joints involved in 27.5 per cent of the men and 19.1 per cent of the women. Next the fingers were most often the first joints affected, and in the women they were almost as frequently

the first involved as were the knees. The fingers were first involved in 24.2 per cent of the women and in 7.3 per cent of the men. In the men, however, the spine, ankles and shoulders were more commonly initially affected than were the fingers.

A tabulation was also made of the joints most severely involved at the time of the examination. The knees again were most often mentioned by 33.3 per cent of the women and 22.7 per cent of the men. The spine was nearly as often the most severely affected in men. It is of significance that the spinal involvement was the most marked in 20 per cent of the men and in only 5.8 per cent of the women. The hips were also much more frequently the joints seriously involved in men (17.3 per cent) than in women (7.1 per cent). However, the fingers were frequently the most severely affected in women (16.6 per cent),

TABLE 1.—*Percentage of Involvement of Individual Joints in Two Sexes*

	Men (110) per Cent	Women (240) per Cent
Fingers	44.5	68.7
Hands	38.2	41.2
Wrists	46.3	51.7
Elbows	40.0	43.3
Shoulders	56.4	57.5
Toes	27.3	37.1
Feet	34.5	27.9
Ankles	56.4	59.6
Knees	77.3	85.4
Hips	50.0	42.1
Spine	69.1	51.7
Sacro-iliacs	29.1	25.8
Jaws	9.1	12.5
Sternoclavicular	3.6	2.0

while in only one man (0.9 per cent) was the involvement of the fingers the most severe.

A comparison was made of unilateral articular involvement in the right and left extremities. There was apparently no significant differences in the right and left lower extremities in any of the groups tabulated. In the upper extremities there was no significant difference between the right and left in the number of joints involved and in the incidence of the joints most severely affected. However, there was an initial involvement of the right upper extremity in 59 cases as compared with 16 cases in which the left upper extremity was first involved. A possible explanation might be that the right upper extremity is usually subjected to greater trauma, and that this may be an inciting factor either in the onset or in the location of the clinical signs of arthritis.

Many general opinions are given as to the frequency of involvement of certain joints in persons in whom arthritis occurs at different ages. A study was made to show the incidence of involvement of joints in men and women separately, the age of onset by decades being considered. In general, it was found that there were few striking differences in the

percentage of involvement of individual joints in the various age groups. The striking sex differences in involvement of the joints are present in nearly all of the age groups. An exception is the observation that the incidence of spinal involvement in women in whom the onset of arthritis occurred between the ages of 20 and 39 years was as great as that in men of that period, while in the age groups 10 to 19 and 40 to 69 there was a marked predominance of involvement of the spine in men. The knees were found to be involved in a higher percentage than other joints in both men and women in all age groups. The fingers were involved in a high percentage of women in all age groups.

There is much discussion of the tendency toward unilateral involvement of the joints among persons acquiring arthritis after 50 years of age. The incidence of unilateral involvement in men and women of various age groups is shown in table 2. Unilateral involvement was found to be more common in women acquiring arthritis in the later decades of life, but no such difference was found in men.

TABLE 2.—*Unilateral Involvement of Joints Tabulated According to Age Groups*

Age Group	Men, per Cent	Women, per Cent
10-19	14	14
20-29	17	10
30-39	19	12
40-49	12	13
50-59	12	18
60-69	..	23

The number of joints involved in each arthritic patient was compared in persons acquiring arthritis in different decades of life. In estimating this factor, the fingers or toes of one side and the joints of a hand or a foot were counted as one joint, as was involvement of the spine. Allowance was made for unilateral and bilateral involvement. There were found to be no striking differences in men in the number of joints affected in each decade, although in women acquiring arthritis in the third and fourth decades there seemed to be a significantly greater number of joints involved than in women of other age groups.

History of "Clinical Rheumatic Fever."—In considering the incidence of rheumatic fever, one is confronted with a difficult problem and much controversy. In general, rheumatic fever is considered as acute involvement in and about the joints, usually polyarticular, which is transitory with associated fever and which subsides within a few weeks or months without the occurrence of permanent articular changes. There is a high incidence of involvement of the endocardium, myocardium and pericardium. Subcutaneous nodules are described in a significant percentage of cases. Rheumatic fever is fairly easily recognized as an entity in children, but it is increasingly difficult to dis-

tinguish it from acute and subacute involvement of the joints with residual changes occurring in adolescence and early adult life. Many such cases in young adults may be diagnosed as rheumatic fever at an early stage of the disease and later as "rheumatoid" (atrophic, proliferative, infectious) arthritis. In young adults in our group such experiences were common. Clinically, I am unable to place a sharp dividing line between cases termed rheumatic fever and those with an apparently similar onset that progress to chronic articular involvement. There are several cases in our group (to be described later) in which there was an acute transitory polyarticular involvement, fever, and a pathologic condition of the heart, with subsequent chronic damage of the joints starting at the time of the acute onset; there are a number of such cases without organic heart disease.

In 45 (12.9 per cent) of my series of 350 cases of chronic arthritis, there was a history of acute polyarticular involvement of the joints with fever and with subsidence of the symptoms in most of the joints within a few weeks or months. A number of these patients had two or more such attacks. In 13 cases there was no definite correlation of the acute attacks and the chronic involvement which appeared a number of years later. In 32 instances the acute attack preceded chronic involvement of the joints. In these instances, there was definite involvement of the heart in 6 cases and questionable involvement in another. All patients with questionable disease of the heart were studied carefully, orthodiagrams or roentgenograms taken at a distance of 6 feet from the patient and electrocardiographic study being employed. Three patients had definite disease of the mitral valves with presystolic murmurs and a contour of the heart characteristic of this condition. One patient, 73 years of age, who had acute involvement of the joints at 58, had a definite aortic insufficiency and a questionable involvement of the mitral valve as well. The Wassermann tests were negative, and there was no history or findings suggesting syphilis. Two persons had definite pericarditis, and one of them showed effusion. Roentgen examination of all of the patients described showed definite articular changes of arthritis. The patient with questionable involvement of the heart was a girl of 17, who had had an intermittent fever for three years which was acute in onset and accompanied by multiple articular pains. She had an average pulse rate of 120 a minute and a systolic murmur, and she was dyspneic on moderate exertion. The orthodiagram, however, was normal in size, and thick barium paste did not demonstrate left auricular enlargement. The incidence of rheumatic involvement of the heart in the 32 patients with chronic arthritis which was acute in onset was 18.7 per cent. There were no other cases of definite rheumatic involvement of the heart in the entire group of arthritic patients whose condition was of more insidious onset, except the case of a patient wtih mitral

stenosis from the group of those who had had acute involvement in the past without correlation with the subsequent chronic involvement. Therefore, the incidence of rheumatic involvement of the heart in the entire group is 7 cases in 350, or 2 per cent. McCrae [11] reported finding valvular heart disease in 40 of 500 cases of chronic arthritis; however, in some of these patients the disease was reported as being of nonrheumatic origin. There were a number of cases of cardiovascular heart disease in this series which were not included in the analysis.

The incidence of heart disease, while very small in the total group, is of some significance in the group of patients with chronic arthritis of acute onset. The ages of onset in this group and the types of condition are respectively as follows: 8, 9, 12, 13, mitral stenosis; 14, a questionable condition; 14, mitral stenosis; 17, 17, 17, 17, pericardial effusion; 18, 18, 19, 19, 20, 21, mitral stenosis; 22, 23, 24, 27, pericarditis; 31, 32, 35, 40, 42, 44, 45, 45, 50, 54, 58, aortic insufficiency and questionable mitral involvement.

The incidence of cardiac involvement in rheumatic fever is the strongest argument for the separation of rheumatic fever and more chronic types of arthritis as disease entities. It seems not unlikely, however, that this may not be a definite point of division, and that the age of the person is an important factor in determining the response of the tissues to similar organisms. There are probably many underlying factors determining the response of tissues to infection that are not well understood. In the case of involvement of the heart valves there is some anatomic basis for the infrequent involvement in older persons. Most investigators are of the opinion that the infection in the heart valves is usually produced by the lodgment of bacteria in the terminal arteries. Gross [19] has presented evidence that the musculature and the blood vessels of the heart valves undergo regressive changes in most persons during childhood, and that such vessels are usually absent in adults. He believes that this may be an important factor in the low incidence of the onset of involvement of the heart valves in older persons. This variation in tissue response seems to be true in nephritis as well as in arthritis, as chronic nephritis persists after acute involvement in about 50 per cent of adults and in only a small percentage of children. In general, in other infections, such as tuberculosis, there are definite differences in the response of the tissues of children and of older persons. The streptococci isolated from the blood, joints and subcutaneous nodules from patients with clinical rheumatic fever and the more chronic types of arthritis are apparently biologically related; in most instances, they exhibit cross-agglutinating reactions and cross-

19. Gross, L.: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, Inc., 1921.

protection in experimental animals. There is also evidence that these streptococci are not unrelated to streptococci causing other manifestations of disease.

The histologic appearance of tissue taken from the subcutaneous nodules of rheumatic and of chronically arthritic patients is similar in structure and not unlike that seen in the valves of the heart affected by acute rheumatism, according to Clawson.[10b] This phase will be discussed in more detail later, but it is mentioned here as a fact which strengthens the probability of a common etiologic basis for rheumatic fever and chronic forms of arthritis.

OTHER FACTORS ASSOCIATED WITH ARTHRITIS

Association of Probable Streptococcic Infection with Arthritis.—Some of the infectious manifestations other than chronic arthritis which may be considered as of probable streptococcic origin are rheumatic fever, chorea, erythema nodosum, myositis, scarlet fever and erysipelas. These conditions do not always occur as entities, and there is some clinical overlapping. Tonsillitis, infections of the roots of the teeth and puerperal sepsis are believed to be due to streptococci. Glomerulonephritis is also considered by many as of streptococcic origin. There was a history of scarlet fever in 57 of 350 cases of arthritis (16.3 per cent). In 2 instances the scarlet fever was a definite forerunner of chronic arthritis indistinguishable clinically from other cases of arthritis. In one of these patients the initial involvement was acute, and now after three years the patient has a definite lesion of the mitral valve, mitral stenosis.

Chorea had been present in only 3 instances in the total series, less than 1 per cent. There was no pathologic condition of the heart in these 3 cases or any definite correlation with the chronic involvement of the joints which appeared later.

According to the histories obtained, dental infection was present in many patients, but it seemed a probable precursor of the arthritis in 17 cases. Such an infection may have been an inciting factor in many more instances, but it was not known to be present to a marked degree in the other cases. The selection of certain cases as being of etiologic significance is of course arbitrary, and after reviewing them, some physicians might believe that the infection was of significance in a much greater number.

Acute sinusitis immediately preceded the involvement of the joints in 13 persons. An acute respiratory infection immediately preceded the arthritis in 11 persons. Such infections were probably present more often and forgotten after a number of years, as most of the histories in which such infections were mentioned were those of patients with a recent onset of articular symptoms.

A history of tonsillitis at some time was present in a large number of patients, but probably in no higher percentage than among nonarthritic persons. In 7 instances, however, the tonsillitis immediately preceded the arthritis; in 3 of them, a peritonsillar abscess was present, and in 1 there was also an associated acute sinusitis.

There was a history of arthritis developing during and persisting following puerperal sepsis in 7 cases. The involvement of the joints was extensive and severe in nearly all of these patients. Arthritis developed immediately post partum in 7 women in whom there was no definite clinical sign of sepsis; in 1 of them thrombophlebitis was present.

There was involvement following other infections, such as peritonitis, erysipelas, erythema nodosum, cervical adenitis and thrombophlebitis. There was a history of some definite infection preceding the arthritic involvement in 70 instances. If the 32 cases are added in which the onset resembled that of acute rheumatic fever, a definite infection preceded the process in the joints in 102 patients or in 29.1 per cent of the total number. In some of these the acute onset was probably preceded by acute infections of the upper part of the respiratory tract, although such a history was given only occasionally.

One point in particular seems worthy of emphasis, namely, that acute infections which may be inciting causes of arthritis may clear up completely in a relatively short period, leaving the patient with infection of the joints which may persist for many years. In a number of cases, the involvement of the joints seemed to be only one evidence of a more general infectious process. Pleuritis, muscular pains, subcutaneous nodules and anemia were not infrequently found when these patients were observed for some time. In the majority of cases, the arthritis was insidious in onset and without a known definite inciting infection. It is true that on thorough search some infection might be found in the teeth, tonsils, sinuses, prostate gland, cervix, gallbladder and intestinal tract, but such infections can likewise be found in many nonarthritic persons. Investigators who have studied the streptococci from the tonsils of arthritic and nonarthritic patients have found no significant differences either in the cultural characteristics or in the incidence of occurrence.

Secondary factors other than a definite infection seem of importance in initiating the clinical symptoms of arthritis. This probably means that these factors allow that opportunist, the streptococcus, to invade the tissues of the joints. Exposure, fatigue and trauma have been given in the history in a number of cases as factors both in inciting and in aggravating the involvement of the joints. Dysfunction of the thyroid gland when present may have some effect on an arthritic process. Neither hyperthyroidism nor hypothyroidism was present in a significant

number of patients in this series. The influence of the menopause has seemed rather vague in our experience; it is true that there is a high incidence of onset of arthritis in women at that period, although it is not relatively higher than in men of the same age. No special type of clinical involvement was recognized in patients acquiring arthritis at that time. Predisposing constitutional factors difficult to evaluate accurately, such as arthritic heredity, asthenic stature, vasomotor constriction and sluggishness of the large bowel, are probably also worthy of consideration. Pemberton [20] is of the opinion that a diet high in carbohydrates may aggravate an arthritic condition.

Trauma as an Inciting Factor.—Trauma has preceded many cases of arthritis. In some instances it has seemed to be a factor in establishing the clinical manifestations of disease of the joints. A history of trauma as a probable inciting cause of arthritis was present in 12 persons. From each there was a history of definite injury, usually to a single joint, which persisted and within a short period of time was followed by multiple articular pains. The probable basis for the arthritis was that the traumatized tissue was more easily invaded by a subsequent infection. The possible rôle of trauma in inciting a clinical arthritic process is further emphasized by the fact that initial involvement of the joints was found to be about the same in the right and in the left lower extremities, while the joints of the right upper extremity were initially involved four times as frequently as those of the left upper extremity. Assuming most persons to be right-handed, trauma should be more frequent and severe in the upper right extremity.

There were many reports of aggravation of arthritic symptoms due to trauma, and in certain cases an occupational traumatic influence was noted.

Subcutaneous Nodules.—Subcutaneous nodules have been reported frequently in the past in clinical rheumatic fever and less frequently in chronic arthritis.

Hillier [21] (1868) was one of the first to describe these lesions. Meynet [22] (1875) first pointed out that they bore a direct relation to acute rheumatic fever. Coates and Coombs [23] considered subcutaneous nodules the specific manifestation of rheumatic fever.

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20. Pemberton, Ralph: Arthritis and Rheumatoid Conditions: Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929.

21. Hillier: Diseases of Children, London, J. Walton, 1868, cited by Jacki, E.: Frankfurt. Ztschr. f. Path. **22**:82, 1919.

22. Meynet, P.: Rheumatisme articulaire subaigu avec production de tumeurs multiples, Lyon méd. **20**:495, 1875.

23. Coates, V., and Coombs, C. F.: Observations on the Rheumatic Nodule, Arch. Dis. Childhood **1**:183, 1926.

Not many observations have been reported concerning the frequency and structure of subcutaneous nodules in patients having chronic arthritis. Hawthorne [24a] described subcutaneous nodules in 6 patients, and he considered rheumatic fever and rheumatoid arthritis as different manifestations of the same process. Garrod [6] also observed subcutaneous nodules in chronic arthritis. Wick [25] saw a relationship between the nodules found in chronic arthritis and those seen in acute rheumatic fever. Subcutaneous nodules in cases of chronic arthritis were also described by Coates and Coombs,[23] Freund,[26] and Dawson and Boots.[24b]

In this series, 300 consecutive patients with chronic arthritis were examined for subcutaneous nodules. The nodules were studied with respect to frequency, location, size, shape, consistence, development and duration. Nodules from 20 patients were removed and examined grossly and microscopically. A portion of each nodule was also cultured for bacterial growth.

Dawson and Boots found that the incidence of subcutaneous nodules in 200 consecutive cases of arthritis was about 20 per cent. Cecil referred to them as being present in from 3 to 4 per cent of the cases.

In our series of 300 patients with chronic arthritis, subcutaneous nodules were found in 94 (31.3 per cent). No attempt was made to determine the frequency of such nodules in any special class of conditions, as I have been unable to recognize distinct divisions, such as rheumatoid arthritis (atrophic, proliferative) and osteo-arthritis (hypertrophic, degenerative). The ages of patients with nodules was determined, and there was a very high incidence of involvement in the older age groups, 54 of the 94 persons with nodules being 50 years of age or more. The condition in many of these older persons would fit the criteria advanced for osteo-arthritis.

The cases in which nodules were found did not fall in any definite group and could not be distinguished in any way from a large number of cases of arthritis without nodules.

Patients were frequently unaware of the presence of nodules; however, in some cases they were painful, especially those located on the plantar surfaces of the feet.

In most cases it is difficult to determine the duration of the nodules. In some instances they were known to have been present for from a

24. (*a*) Hawthorne, C. O.: Rheumatism, Rheumatoid Arthritis and Subcutaneous Nodules, London, J. & A. Churchill, 1900; (*b*) cited by Dawson, M. H., and Boots, R. H.: Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis, J. A. M. A. **95**:1894 (Dec. 20) 1930.

25. Wick, L.: Ein Fall von primären chronischen Gelenkrheumatismus mit subcutanen Knoten, Wien. med. Wchnschr. **31**:1804, 1910.

26. Freund, E.: Ueber rheumatische Knoten bei chronischer Polyarthritis, Wien. Arch. f. inn. Med. **16**:73, 1928.

few months to as long as fifteen years. In general, it has seemed that nodules were of shorter duration in younger persons.

They were distributed chiefly over the extremities, more frequently on the upper extremities than the lower ones. In 5 patients there were nodules over the sacro-iliac joints. There was a frequent tendency toward bilateral distribution. In 94 patients nodules were found in 127 locations, excluding bilateral symmetrical involvement.

The nodules varied in size from 5 mm. or less to 3 cm. All were movable and not attached to the skin, but some were rather firmly adherent to the underlying tissues. Many of the larger nodules were cystic and contained disconnected masses of tissue. The nodules were grossly similar to those occasionally occurring in syphilis, which are referred to as juxta-articular nodules. The experience of my colleagues and myself in a series of patients in the outpatient department has indicated that such nodules are only rarely found in syphilis.

The microscopic appearance of the tissues was studied by Clawson [10b] and found to be chiefly polyblastic in character and similar to the reactions found in subcutaneous nodules and in heart valves in acute rheumatic fever, in the heart valves in subacute rheumatic endocarditis, and in subcutaneous nodules produced experimentally in rabbits by the injection of streptococci. Cultures of the nodules were taken in 17 cases, and streptococci were recovered in 12 instances (70.6 per cent).

ROENTGEN FINDINGS IN ARTHRITIS

Roentgen study has been of much value in determining certain types of changes in the joints which may be present in arthritis, especially destruction of cartilage and bone, atrophy of the bone and the production of new bone. Such study, however, has led to some confusion in diagnosis, as changes in the joints due to various etiologic agents may at times simulate each other, and cases have often been placed in the same class without consideration of the underlying cause. Roentgen study in certain severe clinical types of arthritis also shows little or no change; such is the case in the severe periarticular involvement often seen in children and young adults. Often the diagnosis of the type of arthritis present is withheld until the report on the roentgen examination is available, and then the diagnosis is made according to the change seen in the roentgenogram. The terminology most in use by roentgenologists is that employed in Goldthwait's classification; namely, infectious, atrophic and hypertrophic arthritis. The prominent change in atrophic arthritis was said to be atrophy of the bones adjacent to joints, associated with the destruction of cartilage. Goldthwait expressed the belief that the formation of spicules was indicative of a separate type termed infectious arthritis, although atrophy of the bones and destruction of

cartilage were also said to be prominent in such cases. The characteristic changes in hypertrophic arthritis were said to be formation of new bone, such as lipping, with moderate or little destruction of cartilage and little or no destruction of bone.

There are on record some cases in which roentgenograms have been taken early in the process and the condition classified as atrophic arthritis, and in which a diagnosis of hypertrophic or mixed arthritis has been made later. In considering the roentgen changes, the duration of the lesion and the age of the patient are apparently two important factors. Younger persons frequently have arthritic involvement with negative roentgen findings, while in older persons the roentgen findings are often out of proportion to the symptoms present. The formation of new bone probably represents a rather advanced result of arthritis and may be simulated by other types of change, such as traumatic conditions of the joints in which the destruction of cartilage has taken place, with the subsequent formation of new bone. Senescent changes likewise may simulate true arthritic changes, although such changes in general are apt to be more symmetrical and chiefly present in the spine. The clinical history also is an aid in differentiating such cases from those of true arthritis.

In general, it can be said that the arbitrary selection of one joint for roentgen study and diagnosis of the type of arthritis, is an incomplete method and has led to many errors in classification. With this point in mind, 60 unselected consecutive arthritic patients were thoroughly studied by Dr. Rigler, roentgenologist of the University of Minnesota Hospital. A roentgenogram was made of every joint in which pain was or had been present, and the duration of the involvement was recorded. From this study, it was found that a majority of cases showed more than one accepted type of roentgen change, according to the Goldthwait classification, and that it was possible only to state the type of changes present and the joints involved. Only 33.3 per cent of the patients showed a single type of accepted roentgen change according to the Goldthwait classification; 58.3 per cent showed mixed changes, and 8.3 per cent, none.

Another common source of error in the selection of one or two joints for roentgen examination is that in certain joints, such as the shoulder, so-called atrophic changes are present in nearly all cases, while in such a joint as the knee, hypertrophic changes are much more commonly present. This is particularly significant when one considers that involvement of the knees and shoulders is present in arthritic persons of all age groups in about the same incidence. While roentgen study helps in distinguishing arthritis of streptococcic, gonococcic, tuberculous and syphilitic origin, one cannot make positive etiologic diagnoses in many

cases, and there may be various manifestations of any type of the condition. From an etiologic standpoint, however, the majority of cases seem to be due to streptococcic infection; in general, such a type often tends to involve multiple joints, with varied roentgenographic manifestations. The age of the patient, the duration of symptoms and the joint shown in the roentgenogram are important factors in determining the roentgen changes present in cases of streptococcic arthritis.

PREVIOUS THERAPY

A study has been made of the previous treatment received by the patients in this group. Special attention has been paid to the results of the removal of alleged foci of infection, especially teeth, tonsils and sinuses. A high percentage of patients had received such treatment, and in only a few instances was it followed by much clinical improvement. In many of these cases there was little or no clinical correlation between the arthritis and the possible focus removed. In practically no case of well established or long-standing arthritis was there any improvement following such treatment. This is not difficult to understand when one considers the fact that in such cases the streptococci are probably already well established in the tissues of the joints and in the subcutaneous nodules, which in themselves are sufficient locations for the continuance and further spread of the arthritic infection. It is obvious from the histories alone that this probably occurs in cases of chronic arthritis persisting for years which often follow acute transitory infections. In patients who have had a recent onset of articular symptoms or recurrent symptoms, the results from the removal of supposed foci have been more encouraging; however, in such conditions there is frequently subsidence of symptoms without treatment. In a patient who had not had previous articular symptoms, chronic arthritis developed immediately after tonsillectomy. In several other patients there was a marked aggravation of the symptoms following tonsillectomy or extraction of teeth.

Typhoid vaccine had been administered intravenously to about 60 patients previously; it was found to be of no value in almost every case. A few of the patients so treated reported feeling better for one or two days following the injection, and one patient reported improvement of several months' duration.

The majority of patients had received medication and various forms of physical therapy, with temporary relief in some cases, but in nearly every case without any permanent change in the course of the disease.

Dietary treatments of all types had been tried in many cases, chiefly diets low in carbohydrates, though in other cases diets low in proteins and other special types of diets had been used. Little definite improvement from dietary management alone was reported.

It is difficult to associate arthritis definitely with chronic diseases. The relationship to other infections of streptococcic origin seems clearly established on a clinical basis. Psoriasis is mentioned as being frequently associated with arthritis, and it was found to be present in 5 of 350 cases (1.4 per cent) in our series. Histories of pleurisy and chronic bronchitis were not infrequent, but it was not determined whether such conditions were of greater frequency than in a control group.

LABORATORY DATA

Studies on the Blood.—The blood of 100 consecutive arthritic patients was studied. This study included the hemoglobin determinations and counts of the white and red cells and differential and morphologic studies.

The hemoglobin was less than 70 per cent in 15 per cent of the patients; the incidence of such low readings was significantly greater than was found in the total dispensary group. In 10,000 consecutive dispensary patients, excluding pregnant women, there was an incidence of about 3 per cent with less than 70 per cent hemoglobin. In all cases the hemoglobin has been measured by the same method, with a corrected Sahli hemoglobinometer. The red cell count has not been reduced in proportion to the hemoglobin, and, in general, a low index for hemoglobin was present. There was a more frequent occurrence of moderate leukocytosis in the arthritic patients than in a control series.

Morphologic studies have shown little or no significant changes in either the red or the white cells. Moderate evidences of toxicity in the neutrophils have been manifested in a number of cases, but not in a significant manner.

Wassermann tests of the blood have been made for all patients, and the reaction was found to be positive in very few cases.

Urinalysis.—Urinalysis has been made as a routine in all cases; no significant observations were made which could distinguish the arthritic group from any general group. Diabetes was present in only 3 of the 350 patients in the arthritic group. Transitory glycosuria was not found frequently in this group.

SUMMARY

The analysis has covered a number of clinical phases of arthritis. The sex incidence and age at onset have been determined. The frequency and severity of involvement of individual joints have been tabulated. The clinical relationship of rheumatic fever and chronic arthritis has been considered and a study made of the incidence of organic heart disease in the latter condition. A study has been made of streptococcic infections and trauma as inciting factors in chronic

arthritis. The frequency and distribution of subcutaneous nodules have been determined. The significance of roentgen studies has been discussed. Previous therapeutic methods and results have been reviewed, and a summary of the results of studies of the blood has been made.

A number of persons with transitory pains in the muscles and joints have been omitted from consideration because the study has been limited to patients with symptoms of at least two months' duration. Temporary involvement of various degrees has been observed frequently in persons in the age group from 15 to 30 years. Many cases in which the condition is difficult to class definitely as rheumatic fever or as chronic arthritis occur in these ages. It is my opinion that no sharp line of clinical distinction exists between these conditions at any age, although there are marked clinical differences in selected cases, just as there are marked clinical differences among cases termed chronic arthritis. On the basis of the clinical and the etiologic evidence, it seems likely that streptococcic infection is responsible for the majority of acute and chronic infections of the joints, such as rheumatic fever, rheumatoid arthritis (atrophic, proliferative) and osteo-arthritis (hypertrophic, degenerative). Cases to be excepted from the preceding statement are conditions such as senescent, traumatic and posthemorrhagic changes, which are frequently included under osteo-arthritis. It is to be hoped that an acceptable etiologic classification will be adopted in the near future.

CONCLUSIONS

1. Three hundred and fifty consecutive cases of chronic arthritis have been subjected to a clinical analysis. In this series, 68.57 per cent of the patients were women and 31.43 per cent were men. The peak of onset occurred in the fifth decade for both sexes. The duration of symptoms in this series was over one year in 88 per cent and over five years in 55 per cent of the cases.

2. Monarticular involvement, in a strict sense, was present in only 5 of the 350 cases. A study of the joints involved showed the knees to be affected most frequently in 82.8 per cent of all cases. Other joints commonly involved were the following: fingers, 61.1 per cent; ankles, 58.3 per cent; spine, 57.1 per cent; shoulders, 57.1 per cent; wrists, 50 per cent; hips, 44.6 per cent, and elbows, 42.6 per cent.

3. There are certain definite sex differences in the distribution of the joints affected, there being a significantly more frequent involvement of the fingers, hands, and toes in women and of the spine, hips and feet in men. There is also a marked difference between the sexes in the joints most severely involved, the fingers being the most seriously affected in 16.6 per cent of the women and in only 0.9 per cent of the

men, while, on the other hand, the spine was most severely affected in 20 per cent of the men and in only 5.8 per cent of the women.

4. A study made of the percentage distribution of involvement of the joints by decades showed no striking differences in the distribution in arthritis coming on at different decades of life.

5. In 32 patients with chronic arthritis there was an acute febrile onset which was similar to the clinical description of rheumatic fever. Such an acute onset was much more frequent in the younger age group. Of this number, 6 (18.7 per cent) had definite rheumatic involvement of the heart. The incidence of rheumatic disease of the heart in the total group of 350 patients was 7 (2 per cent).

6. Probable sources of streptococcic infection were known to precede the arthritis in 102 cases (29.1 per cent). The more common inciting sources were dental infection, sinusitis, acute respiratory infection, tonsillitis, puerperal sepsis and the puerperium without known infection. Polyarthritis immediately followed definite trauma in 12 cases.

7. Subcutaneous nodules were sought for in 300 consecutive arthritic patients and were found to be present in 94 cases (31.3 per cent). The incidence of subcutaneous nodules was determined for the various age groups; they were found to be present in over 40 per cent of the patients over 50 years of age. Such nodules were found in patients with various clinical and roentgen findings.

8. Roentgen examinations of all painful joints in 60 consecutive cases have shown a pure type of involvement in only 33.3 per cent, a mixed type in 58.3 per cent and no positive findings in 8.3 per cent of the cases.

EXOGENOUS TUBERCULOUS INFECTION OF ADULTS

MARITAL TUBERCULOSIS

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The susceptibility of adults to the contagion of tuberculosis, a classic subject of controversy, is still under discussion. The disease, many have maintained, does not occur more frequently in adults conspicuously exposed to the disease than in the general population. Statistics from sanatoriums and hospitals for the treatment of tuberculosis have been cited to show that tuberculosis is not unusually frequent in doctors and nurses in constant contact with it. However, in these institutions, suitable precautions, it is true, may be effective in preventing spread of infection. Those who deny the occurrence of exogenous infection of adults base their belief chiefly on the supposed infrequency of obvious marital contagion. If husbands or wives fail to acquire the disease when their consorts suffer with it, there is scant probability that adults are susceptible to infection from without.

Study of the pathologic anatomy has convinced many observers that tuberculosis of adolescence and adult life is a new infection modified by the combination of immunity and hypersusceptibility which follows a first infection acquired, with few exceptions, between infancy and adolescence.

The literature on tuberculosis contains data for an immense collection of statistics concerning marital tuberculosis, in great part based on the histories of parents of persons with tuberculosis. Pearson, in analyzing the histories of 40,000 couples assembled by Pope [1] from the literature on the subject, found scant evidence of marital infection, whereas Arnould,[2] somewhat later, collecting the histories of 53,000 couples, found some evidence of transmission from one consort to another. Nearly every year new studies with varying results are published.

From the Henry Phipps Institute, University of Pennsylvania.

1. Pope, E. G., and Pearson, K.: Drapers' Company Research Memoirs: III. Marital Infection, Department of Applied Mathematics, University College, University of London, 1908.

2. Arnould, E.: Rev. de la tuberc. **6**:177, 1925.

The data contained in this paper are published because (1) they are, with few exceptions, the result of direct observation of married couples continued with varying completeness during periods up to eight years; (2) the studies were conducted with the aid of roentgenologic methods that increase the frequency and accuracy with which pulmonary tuberculosis can be recognized and defined, and (3) the data include observations on latent lesions which, being unaccompanied by significant symptoms or physical signs, preclude the selective examination of those affected.

With the effective application to the examination of the chest of the roentgenologic methods developed in the last decade, the aspect of the problem has wholly changed. It is now possible to recognize pulmonary tuberculosis accompanied by manifest symptoms and physical signs with an accuracy previously impossible, and the scope of such

TABLE 1.—*Occurrence of Clinically Manifest Tuberculosis in White Wives and Husbands After Its Appearance in the Other Marital Partner*

	Number Exposed	Number Not Examined	Number with Tuberculosis	Per Cent with Tuberculosis with Probable Error
Wives exposed to husbands having tuberculosis with				
Tubercle bacilli in sputum	145	45	18	12.4 ± 1.85
No tubercle bacilli in sputum	89	33	4	4.5 ± 1.48
Husbands exposed to wives having tuberculosis with				
Tubercle bacilli in sputum	70	37	9	12.9 ± 2.70
No tubercle bacilli in sputum	72	47	6	8.3 ± 2.19

observations is widely extended by the recognition of lesions unaccompanied by significant symptoms or physical signs and hence designated latent.

The number of married couples studied of whom one or both consorts suffered with tuberculosis was 533; 366 were white (table 1) and 157 Negro (table 7). Since carefully prepared clinical histories were available, it was possible to determine in which marital partner the disease first developed and whether the sputum of this person was known to have contained tubercle bacilli.

When the husband first suffered from pulmonary tuberculosis and had tubercle bacilli in his sputum, tuberculosis appeared in the wife in 12.4 per cent of the cases. When wives first had the disease, manifest pulmonary tuberculosis appeared later in 12.9 per cent of their husbands. It is, then, known to have occurred with approximately equal frequency in husband or wife when the other partner suffered with open tuberculosis.

When the sputum of the person who first became sick with tuberculosis contained no tubercle bacilli at the time when it was examined the incidence of the disease in the marital partner was significantly less, being 4.5 per cent in exposed wives and 8.3 per cent in exposed hus-

bands. There is no reason to doubt that at some time during the association of these husbands and wives tubercle bacilli were discharged in the sputum.

The foregoing figures concerning the incidence of conjugal tuberculosis show how many partners are known to have acquired the disease, but they do not exclude the possibility that the actual number is larger. Of white wives, for example, 234 were exposed to infection by the husband, but of these 78 were not available for examination, and of white husbands a much smaller number presented themselves for examination, so that of 142, more than half, namely, 84, were not examined. It is well recognized that not a few persons with symptoms of pulmonary tuberculosis shun examination because they dread being told that they have tuberculosis. Had it been possible to examine all of these

TABLE 2.—*Occurrence of Latent Apical Tuberculosis in White Wives and Husbands After the Appearance of Tuberculosis in the Other Marital Partner*

	Number Examined and Found to Have No Clinically Manifest Tuberculosis	Number with Latent Apical Tuberculosis	Per Cent with Latent Apical Tuberculosis
Wives exposed to husbands having tuberculosis with			
Tubercle bacilli in sputum	82	21	25.6
No tubercle bacilli in sputum	52	10	19.2
Husbands exposed to wives having tuberculosis with			
Tubercle bacilli in sputum	24	9	37.5
No tubercle bacilli in sputum	19	6	31.6

persons, additional instances of the disease would have been discovered, and the figure representing its incidence would have been increased.

Since latent tuberculosis is unaccompanied by symptoms and unrecognizable by the patient, those with this lesion are no more likely to come to the dispensary for examination than are other persons who have been in contact with tuberculosis. Hence the percentage of latent apical lesions obtained by examination of exposed marital partners with no manifest tuberculosis is equally applicable to those who have failed to report for examination.

Table 2 gives the incidence of latent apical tuberculosis in those wives or husbands who had been exposed to partners with clinically manifest tuberculosis. This enumeration necessarily excludes the exposed partners who had passed through a period of latency and developed clinically manifest tuberculosis.

The latent apical lesions enumerated in table 2 have been classified in table 3 as follows. Group I: Definite but scant lesions recognized immediately below the second rib on one or both sides. Group II: Well defined lesions of which the extent approximates or exceeds half of the apical area above the clavicle. Group III: Lesions that extend below the

clavicle and fall within the definition applied to minimal tuberculosis when the disease is manifest. These lesions are limited to the area above the level of the second chondrosternal junction in front and the fifth vertebral spine behind. When the lesion is densely infiltrated or there is a cavity, it is regarded as a moderately advanced latent lesion and placed in group IV. Group IV: Lesions that exceed those of group III, as defined, in extent or severity, and are commonly classified as moderately advanced when clinically manifest.

It is noteworthy that 7 of 21 lesions in persons exposed to patients with sputum-positive tuberculosis extended below the clavicle, and 2 of these were "moderately advanced," whereas only 3 of 16 lesions in persons exposed to patients with sputum-negative tuberculosis extended below the clavicle, and none of them was moderately advanced.

TABLE 3.—*Anatomic Extent of Latent Apical Lesions*

	I	II	III	IV	
	Small Apical Lesions	Lesions Approximating or Exceeding Half Area Above the Clavicle	Apical Lesions Extending Below Clavicle and Not Exceeding Those of Minimal Tuberculosis	Lesions Equivalent to Those of Moderately Advanced Tuberculosis	Total
In wives exposed to					
Sputum-positive tuberculosis	10	6	3	2	21
Sputum-negative tuberculosis	3	5	2	..	10
In husbands exposed to					
Sputum-positive tuberculosis	4	3	2	..	9
Sputum-negative tuberculosis	2	3	1	..	6

Latent apical tuberculosis, like clinically manifest tuberculosis, was more frequent in husbands than in wives exposed to the disease (table 2). As with manifest pulmonary disease, the relation of the latent apical lesion to infection is shown by its greater frequency and severity in persons exposed to partners with tubercle bacilli in the sputum than in those whose partners were not known to have had tubercle bacilli in the sputum (table 3). Nevertheless, when the results of examination of the sputum were negative the presence of tubercle bacilli in the sputum obviously cannot be excluded, because the number of examinations varied widely, and it is probable that tubercle bacilli were present in some instances before the period of our observation.

During the course of the present study husbands and wives in 108 families in which tuberculosis was not known to exist were examined, with the results shown in table 4.

Of the 5 latent apical lesions in wives, 2 were in group I, 2 in group II and 1 in group III. The latent lesion found in a husband fell in group II.

Comparison of tables 2 and 4 shows that latent apical tuberculosis is far more common in marital partners exposed to tuberculosis than in those with no known contact with the disease. A general summary of the observations that we have made on latent apical tuberculosis is given in table 5. The probability that this is a chance difference is 0.00023 in 100, or approximately 1 to 500,000.[3]

Of 145 wives exposed to open tuberculosis in the husband 18 (table 1) had clinically manifest tuberculosis, which leaves 127, of whom 82 were examined by means of roentgenographic films of the chest. Of this number 21, or 25.6 per cent (table 2), were found to have latent apical tuberculosis. There is no reason to doubt that latent apical

TABLE 4.—*Occurrence of Latent Apical Tuberculosis in White Wives and Husbands with No Known Contact with Tuberculosis*

	Number Examined	Number with Latent Apical Tuberculosis	Per Cent with Latent Apical Tuberculosis
Wives	95	5	5.3
Husbands	47	1	2.1
Total	142	6	4.2

TABLE 5.—*Persons with Latent Apical Tuberculosis*

	Number Examined	Number with Latent Apical Tuberculosis	Per Cent with Latent Apical Tuberculosis and Probable Error
Exposed to tuberculosis in husband or wife	177	46	25.99 ± 2.22
With no known exposure to tuberculosis	142	6	4.23 ± 1.62

tuberculosis and perhaps manifest tuberculosis in addition occurred in at least an equal percentage of those that were not examined, namely, in 25.6 per cent of 45, or 11. The total number of those who may be assumed to have had latent apical tuberculous lesions is 32, or 35.5 per cent. The same estimate applied to other figures of tables 1 and 2 gives the results shown in table 6.

It is commonly assumed that the incidence of clinically recognizable tuberculosis in the general population is approximately 1 per cent; that of latent apical tuberculosis in husbands and wives with no familial contact with tuberculosis was 4.2 per cent (table 4). Hence the frequency of adult types of tuberculous infection in those exposed to the disease by marital contact as shown by the figures in table 6 is comparable to an incidence of approximately 5 per cent in husbands and wives with no known familial contact with tuberculosis.

3. Miss Marjorie Gooch made this estimate.

Table 7 shows the frequency with which calcified lesions of a first infection occur as recognizable nodules in lungs or tracheobronchial lymph nodes of wives and husbands exposed to marital contact with tuberculosis. It is noteworthy that roentgenographic films reveal only

TABLE 6.—*Incidence of Adult Type of Tuberculous Infection in Wives or Husbands After the Appearance of Clinically Manifest Tuberculosis in Other Marital Partner*

	Per Cent with Manifest Tuberculosis	Estimated per Cent with Latent Apical Tuberculosis	Estimated per Cent with Both Forms of Tuberculosis
Wives in contact with husbands having tuberculosis with			
Tubercle bacilli in sputum	12.4	23.1	35.5
No tubercle bacilli in sputum	4.5	18.4	22.9
Husbands in contact with wives having tuberculosis with			
Tubercle bacilli in sputum	12.9	32.7	45.6
No tubercle bacilli in sputum	8.3	27.6	35.9

TABLE 7.—*Incidence of Calcified Lesions of First Infection Found in Lungs and Tracheobronchial Lymph Nodes of Wives or Husbands*

	Number Examined	Lesions of First Infection Found	Per Cent of Lesions of First Infection Found
Wives in contact with husbands having tuberculosis with			
Tubercle bacilli in sputum	82	27	32.9
No tubercle bacilli in sputum	52	10	17.2
Wives with no known contact with tuberculosis	95	21	22.1
Husbands in contact with wives having tuberculosis with			
Tubercle bacilli in sputum	24	5	20.8
No tubercle bacilli in sputum	19	2	10.6
Husbands with no known contact with tuberculosis	47	9	19.2

TABLE 8.—*Occurrence of Clinically Manifest and Latent Apical Tuberculosis in Negro Wives or Husbands After Its Appearance in the Other Marital Partner*

	Number Exposed	Number with Manifest Tuberculosis	Number with No Manifest Tuberculosis That Were Examined	Number with Latent Apical Tuberculosis
Wives in contact with husband having tuberculosis with				
Tubercle bacilli in sputum	79	2	24	2
No tubercle bacilli in sputum	21	0	4	0
Husbands in contact with wives having tuberculosis with				
Tubercle bacilli in sputum	51	2	18	2
No tubercle bacilli in sputum	5	1	3	1

a part of the calcified lesions of the childhood type demonstrable in lungs examined at autopsy (Miller).[4]

These figures, which are very small in some of the groups, suggest that marital contact with tuberculosis may perhaps increase the frequency of lesions of first infection, but the preponderance of infection with marital contact on the one hand and with no known familial association with tuberculosis on the other is far less than in adult types of infection in the corresponding groups of married persons.

The number of married couples of the Negro race under observation has been too small to give satisfactory information concerning the incidence of tuberculosis in the marital partners of tuberculous persons of this race. It has been possible to follow few families continuously, and men especially fail to seek medical care until their disease is advanced. The figures in table 8 are cited in order to show the difficulty of collecting under unfavorable conditions information concerning marital tuberculosis.

Of the latent apical lesions found in wives, one was represented by a scant shadow occupying approximately half of the apex above the clavicle (group II) and the other extended from above below the clavicle (group III). Of the latent apical lesions of husbands, 2 were represented by scant shadows below the second rib (group I) and 1 extended from above below the clavicle (group III).

CONCLUSIONS

When roentgenographic methods are used for the recognition of tuberculous lesions of the lungs in husbands and wives in contact with a tuberculous partner, exogenous infection of adults is clearly demonstrable.

Husbands and wives in marital contact with tuberculosis under varying conditions are infected from five to nine times as often as persons with no known contact with the disease; husbands are infected oftener than wives.

The frequency of infection in wives exposed to husbands with tubercle bacilli in the sputum was 35.5 per cent; in those exposed to husbands with no demonstrable tubercle bacilli, 22.9 per cent. The incidence of infection in husbands exposed to wives with open tuberculosis was 45.6 per cent, and when there were no tubercle bacilli in the sputum it was 35.9 per cent.

When the incidence of latent apical tuberculosis in persons exposed to tuberculosis in husband or wife is compared with that in husbands or wives with no known exposure to tuberculosis, the possibility that the difference has occurred by chance is negligible.

4. Miller, G. R.: Am. J. Roentgenol. **36**:191, 1931.

NORMAL RENAL THRESHOLD FOR DEXTROSE

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The results of experiments performed solely to determine, as nearly as clinically possible, the normal renal threshold for dextrose are reported in this paper.

Most of the previous information on this subject has been gleaned incidentally during the study of dextrose tolerance curves. A great many of the patients studied were hospital patients. The various values reported led us to attempt to discover the renal threshold in normal persons. We believe that while there are small amounts of reducing substances in the urine most of the time, there is a definite threshold level at which large quantities of dextrose are excreted in the urine. This is shown in numerous cases by an abrupt appearance of heavy precipitate when a series of successive specimens of urine are tested with Benedict's solution while the blood sugar is rising after the ingestion of a large quantity of dextrose.

The normal renal threshold has been variously given in textbooks and papers since Jacobsen's [1] article in 1913. He reported values of from 160 to 170 mg. per hundred cubic centimeters; Hamman and Hirschman [2] (1917) and Todd and Sanford [3] (1930) both reported values from 170 to 180 mg.; Osgood and Haskins [4] (1931), from 170 to 190 mg.; Stitt [5] (1927) and Hawk and Bergeim [6] (1927), from 160 to 180

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1. Jacobsen, A. T. B.: Untersuchungen über den Einfluss verschiedener Nährungsmittel auf den Blutzucker bei normalen, zuckerkranken und graviden Personen, Biochem. Ztschr. **56**:471, 1913.

2. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar, Arch. Int. Med. **20**:761 (Nov.) 1917.

3. Todd, J. C., and Sanford, A. H.: A Textbook of Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1930, p. 345.

4. Osgood, E. E., and Haskins, H. D.: A Textbook of Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Company, 1931, p. 54.

5. Stitt, E. R.: A Textbook of Practical Bacteriology, Blood Work, and Animal Parasitology, Philadelphia, P. Blakiston's Son & Company, 1927, p. 728.

6. Hawk, P. B., and Bergeim, O.: A Textbook of Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Company, 1927.

mg., and Cummer [7] (1926), over 200 mg. Johns [8] (1930) expressed the belief that all of these values are too high, and that there is "no such thing as a normal threshold but that for all individuals there is an individual threshold." Eight of the fourteen cases of Goto and Kuno [9] (1921) showed values below 160 mg. Mackay [10] (1927) found cases that did not show glycosuria when the blood sugar was over 200 mg. for some time. Glassberg,[11] during studies on arteriovenous blood, found two cases with variable renal thresholds. Additional references only add greater confusion to these figures.

METHODS

Many of the variations in values may be accounted for by the use of different methods of determining the blood sugar level. To be sure of the best method of determining the true blood sugar, it was first found that a 10 per cent yeast suspension will remove all the fermentable sugar in fifteen minutes, as stated by Somogyi [12] (1927). The blood sugar of twenty-five normal and dispensary patients was determined on filtrates prepared (1) by the Folin-Wu tungstate precipitating method, (2) by the zinc sulphate-sodium hydroxide method of Somogyi [13] and (3) by tungstate precipitation after fermentation with 10 per cent yeast suspension. The results thus obtained are shown in table 1. The average nonfermentable substance was 21.2 mg. per hundred cubic centimeters despite the presence of disease. There was a variation of from 11 to 32 mg. per hundred cubic centimeters, 90 per cent of the cases varying from 17 to 28 mg. When the zinc sulphate-sodium hydroxide precipitation method was used, there was a deviation from the true sugar value of ∓ 7 mg. per hundred cubic centimeters, as shown by the results of the tungstate method minus those of the combined yeast and tungstate method. With this method, the results ranged from 9 to 27 mg. lower than with the tungstate method, with an average of 20.2 mg. On the basis of these findings, it was decided to use the zinc sulphate-sodium hydroxide method of precipitating the blood proteins, and, for comparison with most of the older figures, to add to the results 21 mg. per hundred cubic centimeters. In this we defer to Somogyi's [14] larger series and avoid splitting milligrams.

To determine the sugar in the filtrate, Haskins and Holbrook's [15] modification of the Shaffer-Hartman method was used.

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7. Cummer, C. L.: A Textbook of Clinical Laboratory Methods, Philadelphia, Lea & Febiger, 1926, p. 254.

8. Johns, H. J.: A Study of One Thousand One Hundred Glucose Tolerance Tests, M. J. & Rec. **131**:287, 351 and 398, 1930.

9. Goto, K., and Kuno, N.: Studies on the Renal Threshold for Glucose, Arch. Int. Med. **27**:224 (Feb.) 1921.

10. Mackay, H. L.: Observations on the Renal Threshold for Glucose, Biochem. J. **21**:760, 1927.

11. Glassberg, B. Y.: Kidney Threshold for Glucose in Diabetic and Non-Diabetic Persons, J. Lab. & Clin. Med. **16**:948, 1931.

12. Somogyi, M.: The Reducing Non-Sugars and True Sugar in Human Blood, J. Biol. Chem. **75**:33, 1927.

13. Somogyi, M.: A Method for the Preparation of Blood Filtrates for the Determination of Sugar, J. Biol. Chem. **86**:655, 1930.

14. Somogyi, M.: The Nature of Blood Sugar, J. Biol. Chem. **80**:733, 1928.

15. Osgood, E. E., and Haskins, H. D.: A Textbook of Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Company, 1931, pp. 291 and 263.

EXPERIMENTS

Healthy male medical students between the ages of 20 and 32 were used. In none of these had glycosuria been detected previously.

1. Varying amounts of dextrose were given, starting with 150 Gm. in a 50 per cent solution and increasing to 300 Gm. In five of six subjects who were given 300 Gm., positive results were obtained; but since one subject suffered a gastric hemorrhage, the amount was reduced to 250 Gm., and no more accidents occurred.

2. After the dextrose was given, the subject was asked to urinate every five minutes. A control specimen taken before the experiment and those taken during

TABLE 1.—*A Comparison of the Tungstate, Zinc Sulphate-Sodium Hydroxide and a Combination of the Yeast and Tungstate Methods for Determining Blood Sugar*

Number	Tungstate Method, Mg. per 100 Cc.	Yeast Plus Tungstate, Mg. per 100 Cc.	True Sugar, Mg. per 100 Cc.	Zinc Sulphate-Sodium Hydroxide Method, Mg. per 100 Cc.	Deviation of Zinc Sulphate-Sodium Hydroxide from True Sugar, Mg.	Red Cell Count	Source
1	127	19	108	112	+4	1,910,000	M.C.H.*
2	112	11	101	103	+2	2,950,000	M.C.H.
3	80	17	63	65	+2	3,250,000	Clinic
4	97	17	80	73	−7	4,000,000	Clinic
5	88	19	69	69	0	4,100,000	Clinic
6	123	24	99	104	+5	4,520,000	Clinic
7	99	18	81	78	−3	4,560,000	Clinic
8	88	19	69	68	−1	4,800,000	Clinic
9	87	20	67	70	+3	4,900,000	Clinic
10	70	21	49	48	−1	5,100,000	Clinic
11	104	17	87	87	0	5,550,000	Clinic
12	109	28	81	83	+2	5,840,000	Clinic
13	85	20	65	72	+7	6,650,000	Clinic
14	123	32	91	96	+5	Not determined	Clinic
15	99	21	78	76	−2	Not determined	Clinic
16	282	25	257	257	0	Not determined	Clinic
17	90	24	66	65	−1	Not determined	Clinic
18	77	21	56	59	+3	Not determined	Clinic
19	117	23	94	98	+4	Not determined	Clinic
20	158	22	136	138	+2	Not determined	Clinic
21	114	20	94	87	−7	Not determined	Clinic
22	98	22	76	78	+2	Normal	
23	95	25	70	76	+6	Normal	
24	89	24	65	66	+1	Normal	
25	99	22	77	77	0	Normal	
Average		21.2			−1		
Variation		11 to 32			−7 to +7		

* Multnomah County Hospital.

it were boiled for two minutes in Benedict's solution directly over a flame. When the test became faintly positive, venous blood was drawn. The time elapsing between urination and the completed withdrawal of the blood averaged about five minutes. The time required for the urine to reach the bladder could not be measured.

3. In several cases that did not show glycosuria, blood was drawn at thirty and forty-five minutes to determine the maximum blood sugar level attained.

4. No special preparation by the subject was required. He was advised to drink a great deal of water before the experiment. Most of the tests were made at noon. Only four patients were unable to urinate as required, and no blood was taken from them. Urination in a few of the others was somewhat irregular, but unless the urine five minutes preceding the final positive specimen was negative, the results were not used.

RESULTS

Thirty-four persons were tested; four could not urinate; eight did not have glycosuria, and twenty-two gave satisfactory results. Three of those who did not have glycosuria were given a larger amount of dextrose, and two then excreted sugar, making a total of twenty-four satisfactory tests. In five cases in which the threshold had been established,

TABLE 2.—*Renal Threshold for Dextrose in Twenty-Four Normal Subjects*

Number	Dextrose Given, Gm.	True Sugar,* Mg. per 100 Cc.	Estimated† Tungstate Value, Mg. per 100 Cc.	Minutes
1	250	99	120	35
1	250	122	143	35
2	250	117	138	30
2	250	137	158	30
3	250	123	144	35
4	250	134	155	35
4	250	No glycosuria		
5	250	142	163	35
6	150	146	167	20
6	150	131	152	25
7	250	146	167	35
8	300	148	169	30
9	150	151	172	30
10	300	151	172	40
11	300	151	172	45
12	300	151	172	30
13	150	152	173	25
13	150	No glycosuria		
14	200	157	178	30
15	250	158	179	35
16	250	158	179	25
17	200	160	181	30
18	250	167	188	35
19	250	168	189	35
20	300	172	193	35
21	250	180	201	30
22	250	180	201	40
23	275	188	209	45
24	250	228	249	30
Average		155.3	175.3	33
Mean		151 to 152	172 to 173	35
Range		99 to 228	120 to 249	20 to 45

* Determined by zinc sulphate-sodium hydroxide method.
† Estimated by the addition of 21 mg. to the true sugar values.

tests were repeated with the same amount of dextrose; only three of these again showed glycosuria. Table 2 gives the threshold values as obtained, from the lowest to the highest.

For the sake of clarity and brevity, the true figure for sugar will first be given, followed in parenthesis by the estimated value of the tungstate precipitation method. The lowest threshold for sugar found was 99 (120) mg. per hundred cubic centimeters, and the highest, 228 (249) mg. The arithmetical average was 155 (176) mg., and the mean, from

151 to 152 (172 to 173) mg. The values in 80 per cent of the cases fell between 140 (160) mg. and 190 (210) mg. per hundred cubic centimeters. The threshold for one subject was found to vary as much as 23 mg. per hundred cubic centimeters. Two others showed variations rather large to be accounted for by experimental error.

The results in six of the eight cases not showing glycosuria, but in which samples of blood were again taken thirty and forty-five minutes after the initial withdrawal of venous blood, are shown in table 3.

The purpose of this table is to show the maximum blood sugar level attained without glycosuria and to give some indication of the reaction of healthy persons to large quantities of dextrose. In every case but one the blood sugar level was definitely lowered after forty-five minutes, but in this case it had not yet risen above 100 mg. per hundred cubic centimeters at the end of this period.

TABLE 3.—*True Blood Sugar Values of Subjects Without Glycosuria*

Number	Dextrose Ingested, Gm.	30 Minutes	45 Minutes
25	200	117	76
26	280	156	134
27	260	153	132
28	270	161	133
29	250	134	106
30	250	82	99

COMMENT

While this series is not as large as we should like, it clearly shows that there is a marked variation in the normal renal threshold for dextrose, and that the threshold varies in the same person. Values in a small series of five or six subjects might easily range below or above the figures quoted here. Also, if one were to use tungstate as the precipitating agent and the Shaffer-Hartman titration method, the threshold would appear 21 mg. per hundred cubic centimeters higher than the true figures for dextrose. Methods yielding results between those of the methods used here and the older, more inaccurate methods have added still greater confusion to the literature.

Of the four cases with thresholds below 140 (160) mg., it may be said that in each, several twenty-four hour urines were tested and none gave reduction. In this test, 250 Gm. of dextrose was needed by three subjects to raise the blood sugar level sufficiently to cause glycosuria, even though their thresholds appeared much lower than normal. It seems from this that something more than a mere lowered threshold is present in renal glycosuria, and that some persons have a compensatory mechanism that enables them to utilize dextrose so that its content in the blood never rises high enough for excretion in the urine.

In two cases in which the experiment was repeated with an added amount of dextrose and in which glycosuria showed on the second test,

samples of blood had been taken during the previous test. In one, the blood sugar was 139 mg. per hundred cubic centimeters, with no glycosuria. When the renal threshold was determined, it was 148 mg. In the other subject, the first sample was 128 mg., and the threshold was 134 mg. per hundred cubic centimeters. This tends to indicate that in these cases the threshold was at a definite level, and that an accurate estimation was obtained.

When Benedict's solution and urine are boiled directly over a flame, a sediment frequently collects that makes detection of a yellow precipitate difficult. In several doubtful cases the sugar in the urine was determined by the Shaffer-Hartman method, and unless there were total reducing substances equivalent to 0.3 Gm. or more of dextrose per hundred cubic centimeters of urine, the tests were not considered positive.

The probable error calculated for this series is 15.5 mg. Three times this value either side of the mean should include 95 per cent of all possible cases, as should any stated normal range. This would give a variation of 47 mg. from the mean, or a range from 105 to 200 (125 to 220) mg. per hundred cubic centimeters. Careful scrutiny of the results in table 2 will show that most of the results are grouped about the mean, that the mean is the most frequently occurring figure, and that the series falls within these limits except in two cases. A series presenting these characteristics should be representative of results to be obtained from a larger series.

SUMMARY

1. Filtrates obtained by Somogyi's zinc sulphate-sodium hydroxide method of precipitating blood proteins give true sugar values within a range of ±7 mg. per hundred cubic centimeters.

2. Filtrates obtained by the tungstate precipitation method give results within a narrow range, averaging 21 mg. higher than the true sugar; hence, tungstate methods are clinically satisfactory, and this factor, 21 mg., can be used to transpose results from one method to the other.

3. It seems to be impossible to produce an alimentary glycosuria in some normal persons by the ingestion of large amounts of dextrose.

4. The renal threshold for true sugar varies from 99 to 228 mg. per hundred cubic centimeters, 80 per cent of cases having values that range from 140 to 190 mg.

5. If a normal renal threshold is to be given, it must allow for wide variation. We suggest, from the probable error of 15.5 mg. and the mean of 151 mg. of this series, a probable range of from 105 to 200 mg. for true sugar, or from 125 to 220 mg. if the tungstate precipitation method is used.

Book Reviews

Blood Sugar in Normal and Sick Children with Special Reference to Coeliac Disease. By Elisabeth Svensgaard. Acta pædiatrica, volume 12, supplement 4, 1931.

This rather lengthy dissertation on blood sugar values is prepared in three parts. The first deals with the reports in the literature concerning blood sugar values in normal adults, which have been determined by various authors and with various methods. The author points out that these values are not constant from day to day or from hour to hour, and that there may be slight variations due to emotions and physical exertion.

Alimentary hyperglycemia in adults has been studied for the most part by the administration of from 1 to 2 Gm. of dextrose per kilogram of body weight. This results in a maximal blood sugar value at from one-half to one hour, the figures ranging from 0.13 to 0.18 per cent. This rise subsides within the following two and a half hours, and any rise remaining after three hours is considered pathologic. There may be a subsequent hypoglycemia with blood sugar values as low as 0.05 per cent below fasting values.

Some authors report a slight variation from the fifth to the ninth decade of life. A preceding diet that is high in protein and fat and low in carbohydrate lowers the tolerance for subsequent carbohydrate; that is, a higher and more protracted hyperglycemia occurs.

A prolonged fasting period preceding the dextrose tolerance test gives values from three to four times as high as are obtained with a starvation period of relatively short duration. Muscular activity before the test has no influence, but during the test may give a lower curve. Nausea during the test may result in a decrease in the alimentary hyperglycemia.

The amount of dextrose administered has no effect on the rise of the blood sugar. Large doses, amounting to 250 Gm. and more, give a somewhat longer period of the high level, and usually the level does not return to normal as soon as with ordinary doses. Minimal doses, for example, 0.33 Gm. per kilogram, give a small rise, but as little as 0.5 Gm. per kilogram will give the usual curve. Repeated ingestions of dextrose result in a hyperglycemia only from the first dose. The hyperglycemia subsides even when dextrose is still present in the stomach. It has been found that 10 per cent dextrose is apt to leave the stomach more rapidly than a solution of higher or lower concentration. The blood sugar curve on different days for the same person may vary as much as 0.047 per cent, and the duration of the hyperglycemia curve may vary as much as forty-five minutes.

The second part of the report deals with observations on blood sugar in normal children as reported by others and with the results of the author's researches along these lines. According to other observers, the fasting blood sugar values range from 0.074 to 0.103 per cent. The tests were made at times that differ in relation to meals. Fasting periods under three hours are followed by many values above 0.100 per cent. Fasting periods longer than four hours result in values mostly under 0.100 per cent. On the whole, after four hours or more of fasting the blood sugar values have been found slightly lower in children than in adults, that is, from 0.080 to 0.085 per cent. In premature infants extremely low values have been reported, from 0.030 to 0.070 per cent. After protracted fasting periods of from one to several days the reports show a great variation. There has been no emotional influence demonstrated on blood sugar values in children.

The review of the blood sugar values after the ingestion of dextrose includes only those obtained from capillary and arterial blood, the results ranging from 0.029 to 0.057 per cent greater than in studies made on venous blood. Some authors reported that in children under 1 year of age the rise in blood sugar concentra-

tion in alimentary hyperglycemia follows within the same limits as in adults. Maximal values appear within from one-half to one hour, the duration of the alimentary hyperglycemia being less than three hours. The influence of protracted fasting on alimentary hyperglycemia in children has been found to be the same in two respects as in adults; namely, the carbohydrate tolerance is lower after protracted fasting, and a period of high protein and fat diet is followed by a lowered carbohydrate tolerance.

The author studied several groups of children. The first consisted of eleven new-born infants, from 4 to 14 days of age, on whom twenty-two examinations were done. The fasting period was from five to five and one-half hours, and the average fasting blood sugar value was 0.083 per cent, the values ranging from 0.066 to 0.099 per cent.

The second group was composed of twenty infants, from 15 days to 1 year of age, on whom forty-six examinations were made, the fasting period lasting from six to six and one-half hours. The average fasting value was found to be 0.080 per cent, with a range from 0.067 to 0.101 per cent. The third group was composed of six children, aged from 1 to 8 months, on whom twelve examinations were made. The fasting period lasted from six to six and one-half hours, and in this group saccharose was given in place of dextrose. The average fasting value was again found to be 0.080 per cent, with a range from 0.062 to 0.089 per cent. The fourth group consisted of twenty-two children, from 1 to 13 years of age, on whom forty-three examinations were made. The fasting period was from fourteen to fifteen hours. The average fasting value was 0.088 per cent, the values ranging from 0.068 to 0.099 per cent.

The author therefore concludes that in the first two weeks of life and in the first year of life there is a tendency to fasting blood sugar values which are lower than those in adults. In older children the values are the same as those usually observed in normal adults. The hyperglycemia is generally somewhat greater after the ingestion of dextrose; after saccharin, however, the reverse has been found. In six children, aged from 2 weeks to 3½ years, examinations were made after definite doses of dextrose, ranging from 1 to 10 Gm. per kilogram of body weight. The so-called acceleration phenomenon was found to appear, but apparently at somewhat higher blood sugar values than in adults.

The author then reports observations made on blood sugar values in groups of children with celiac disease, cretinism, eczema, rickets and tetany. No observations were made on diabetic children. The clinical features of celiac disease, together with results of observations on blood sugar values as reported by other authors, were given. Svensgaard's investigations showed that none of the children whom she studied showed abnormalities of the fasting blood sugar values. The average fasting value was 0.085 per cent, with variations from 0.070 to 0.097 per cent.

The results of her study showed that in patients with celiac disease there is a tendency to an exceedingly slight hyperglycemia after the ingestion of dextrose. This peculiarity of blood sugar regulation appears remarkably constant in tests at intervals even of months and years, and even when these patients are examined during periods of definite improvement. A low blood sugar cure is therefore to be regarded as a sign of diagnostic importance in celiac disease. The author postulates that the slight alimentary hyperglycemia in celiac disease cannot be due primarily to an abnormality of the carbohydrate metabolism, but that it is a secondary result of an abnormality in fat metabolism. The low blood sugar curve may then be due to an unusually rapid assimilation of the dextrose absorbed.

A review of the blood sugar values as found in myxedema and hyperthyroidism precedes the report of the author's investigation on blood sugar in cretins. She found that in cretinism the ingestion of dextrose gives only a rather low rise of the blood sugar curve, but that after treatment ingestion of the same dose of dextrose gives an extremely marked degree of hyperglycemia.

After reviewing the reported blood sugar studies in eczema, her own investigations are presented. In these children, after the ingestion of dextrose, she found a maximal value above 200 mg. per hundred cubic centimeters somewhat more

frequently than in normal persons, but except for this rise, the blood sugar curve did not exceed the maximal values frequently found in normal children.

In rickets and tetany, in contrast to reports of others, she found a normal alimentary hyperglycemia curve. She points out that all of the cases of tetany were complicated by rickets, which might conceal a possible difference in the blood sugar regulation. In tetany she found the fasting blood sugar values generally very low, less than 0.070 per cent, but after ingestion of dextrose there was a normal blood sugar curve, indicating that there was no radical change in the blood sugar regulation.

Classic Descriptions of Disease. By Ralph H. Major, M.D., Professor of Medicine, University of Kansas School of Medicine. Price, $4.50. Pp. 630, with 130 illustrations. Springfield, Ill.: Charles C. Thomas, 1932.

This book introduces one to the history of internal medicine in a most attractive manner. It republishes the original descriptions of many familiar clinical entities, methods of clinical diagnosis and methods of treatment. Practically the entire field of medicine and its development are covered from Hippocrates, with his description of the Hippocratic facies, to such recent work as the description of the early experiments with the use of insulin by Banting and Best, or the results of the administration of liver to the first group of patients with pernicious anemia so treated and reported by Minot. Each author mentioned has been selected carefully and represents a physician who has contributed observations of fundamental importance to the growth of knowledge in some particular field of internal medicine, and each quotation has been well chosen and is labeled with an accurate reference stating where the original is to be found. A short, lively, biographic sketch of each author accompanies his work, and often, also, a picture to give some idea of his appearance.

Dr. Major remarks in the preface to the book that the value of referring students to classic accounts of disease has been stressed by many of the greatest clinicians. His book is bound to be extremely useful to all teachers who believe in carrying on this method of instruction, and to all students with any historical bent. Naturally, by virtue of the material contained in it, the volume is filled with good writing. It makes a fine addition to any library.

Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritus. By Louis A. Buie. Cloth. Price, $3.50. Pp. 178. Philadelphia: W. B. Saunders Company, 1931.

The Mayo Clinic monograph on proctoscopic examination describes the methods of diagnosis and treatment of the rectal diseases at the Clinic. The first three chapters explain in detail their various instruments and methods of examining patients.

Under "Etiology of Hemorrhoids" the author considers the various factors and is of the opinion that infection plays the important rôle. Other proctologists believe that physical factors play a much more important part. The author considers sacral block as the anesthesia of choice because of better relaxation. From the reviewer's experience, complete relaxation can be obtained by circular infiltration with procaine hydrochloride. The chapter on "Hemorrhoidectomy" carefully describes the surgical procedures used by the author, and stresses the importance of postoperative care. Under "Treatment by Nonsurgical Methods" the technic is explained, along with the various solutions used and the complications following this method of treatment of hemorrhoids.

The various theories of pruritus ani are presented, along with the histopathologic changes. The author reports 84 per cent cures by the injection of 40 per cent ethyl alcohol subcutaneously, and stresses the importance of the care of the sloughing, which, he states, will accompany about half the injections. When used by inexperienced physicians, the dangers of such treatment are the extensive sloughing and stricture formation.

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